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Abstracts of Papers and Posters Presented at the International Anesthesia Research Society 63rd Congress

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Journal of the International Anesthesia Research Society

Title: THE ATTENUATION OF A POST DURAL PUNCTURE HEADACHE WITH A PROPHYLACTIC BLOOD PATCH IN LABOR PATIENTS

Authors: W.E. Ackerman, M.D., M.M. Juneja, M.D., D.M. Kaczorowski, D.O.
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Introduction. A retrospective study has found that a prophylactic epidural blood patch (PEBP) administered immediately after delivery attenuates the incidence of postdural headaches (PDH) in pregnant patients who had sustained an accidental tear in the dura during epidural needle placement. The study is a randomized prospective study to evaluate the efficacy of performing a PEBP immediately post partum.

Methods. Institutional Review Board approval and patient consent were obtained from all patients. Fourteen healthy ASA I or II patients who had requested epidural analgesia for labor and who sustained inadvertent dural tears during needle placement were divided into two groups of 7 patients. All patients had their epidural catheters replaced one interspace above the dural puncture. Group I, designated as the control, did not receive a prophylactic blood patch. Group II had 18-20 ml of autologous blood administered through the epidural catheter immediately post partum. The patients were asked to rate their headaches on a scale of 0-2 (0=no headache; 1=mild headache; 2=severe headache). Headaches with a scale of 2 received a blood patch. The patients were each followed for 5 days to observe for the incidence of a dural puncture headache. All dural tears were done with a 17g Tuohy needle. Statistical analysis of quantitative data was analyzed using the Student's t test. Statistical analysis of qualitative data was done using the Chi squared test. Statistical significance is $p < 0.05$.

Results. There were no significant differences in maternal characteristics between the two groups. The incidence of post dural puncture headache was 4/7 (57.1%) in the control group and 1/7 (14.3%) in the prophylactic blood patch group. The patient in the prophylactic blood patch group had a period of 9 hours between the dural tear and the time of the blood patch as opposed to a mean time of 3 hours 56 min (± 29.3 min) for the entire prophylactic blood patch group. Three patients in Group I required a therapeutic blood patch and the one patient in Group II required a blood patch. No patient in either group complained of a headache after a therapeutic blood patch was performed.

Table 1. Study data.

	Group I	Group II
Incidence of headache (N/%)	4/57.1%*	1/14.3%
Patients requiring blood patch for headaches (N/%)	3/42.9%*	1/14.3%

*$p < 0.05$.

Discussion. The incidence of PDH was statistically higher in the control group. Our results demonstrate that a PEBP with a mean volume of 18.6 ± 0.67 ml attenuates the incidence of PDH in parturients who have sustained dural tears with epidural needles. Our data furthermore suggests that the PEBP should be performed less than four hours post tear and is under further investigation at our institution.

Reference

1. Ackerman WE, Colclough GW: Prophylactic epidural blood patch: the controversy continues. Anesth Analg 66:913, 1987.

Title: 2-CHLOROPROCAINE DECREASES THE DURATION OF ANALGESIA OF EPIDURAL FENTANYL

Authors: W.E. Ackerman, M.D., M.M. Juneja, M.D.

Affiliation: Dept. of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267-0531

Introduction. The administration of 50 micrograms of epidural fentanyl is useful for the control of postoperative cesarean section pain (1). It is not uncommon to top up amide epidural anesthetics with 3% 2-chloroprocaine to attain or maintain adequate sensory levels during cesarean sections. The purpose of this study was to determine what effect 3% 2-chloroprocaine, as a top-up dose, had when given in addition to 0.5% bupivacaine on the efficacy of epidural fentanyl for the control of postoperative pain in cesarean section patients.

Methods. After institutional approval and informed consent were obtained, 60 healthy women undergoing cesarean delivery had epidural catheters placed and were assigned to one of four groups. Groups I and II received 15 ml of 0.5% bupivacaine (pH 6.0) with top up doses of 3% 2-chloroprocaine (pH 2.7) to attain a T4 sensory level. Groups III and IV received 0.5% bupivacaine only. Immediately after delivery of the fetus, Groups I and III received 10 ml of saline and Groups II and IV received 50 micrograms of fentanyl (pKa 8.4) dissolved in 9 ml of saline. The duration of analgesia was from the time of administration of the study solution until pain was experienced. Data were compared using analysis of variance, the Tukey, Duncan's multiple range test, and the student t test where indicated. Significance is $p < 0.05$.

Results. There were no differences in maternal characteristics between the groups. The addition of 2-chloroprocaine decreased the duration of analgesia of epidural fentanyl (Table 1).

Table 1. Effects of 2-CP on the duration of analgesia.

Group	Total Vol. of Local Anes. (ml)	Vol. of 3% 2-CP (ml)	Duration of Analgesia (min)
I	24.25 ± 2.88	8.2 ± 2.98	32.55 ± 20.69
II	22.95 ± 3.06	7.7 ± 3.36	107.80 ± 19.07*
III	21.9 ± 1.97		47.6 ± 10.47
IV	22.2 ± 1.81		166.3 ± 18.95*

*$p < 0.05$.

Discussion. The use of 3% 2-chloroprocaine to supplement 0.5% bupivacaine epidural anesthesia adversely affected the duration of epidural fentanyl for the control of post cesarean section pain.

References

1. Naulty JS, Sanjay D, Ostheimer GW, Johnson MD, Burger GA: Epidural fentanyl for post cesarean delivery pain management. Anesthesiology 63:694-698, 1985.

Title: EFFECT OF pH ADJUSTED 2-CHLOROPROCAINE AND POSITION ON ONSET OF EPIDURAL ANALGESIA IN LABOR PATIENTS

Authors: W.E. Ackerman, M.D., M.M. Juneja, M.D., D.M. Kaczorowski, D.O., S. Sarracino, M.D., D.D. Denson, Ph.D., C.J. Nicholson, C.R.N.A., J. Schipper, S.N.A.
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Introduction. The pH adjustment of lidocaine and bupivacaine with sodium bicarbonate has been shown to decrease the onset of epidural blockade (1,2). The purpose of this study was to compare the onset time of epidural 2-chloroprocaine (2CP) with pH adjusted 2CP and to compare what effect pH adjustment with sodium bicarbonate had with respect to epidural onset time in the sitting and lying positions.

Methods. Human Research Committee approval and informed consent were obtained from 40 healthy parturients who had requested epidural analgesia for labor. The epidural catheters were placed at the L2-3 or L3-4 interspaces and were advanced approximately 2.5 cm. All epidural catheter placements were done with a loss of resistance technique using air and with the patient in the sitting position. The patients were randomly assigned to one of four groups. Group I received 2% 2CP with each patient lying left side down. Group II received 2 CP buffered with $NaHCO_3$ (3 mEq/30 ml) with each patient lying left side down. Group III received 2CP in the sitting position and Group IV received buffered 2CP in the sitting position. With each patient, 3 ml of study solution was administered through the catheter as a test dose followed by a latency period of two minutes. Subsequently, 5 ml of epidural study solution were administered. The posterior S2-3 dermatomes were tested for analgesia to pinprick at time 0 and every 30 seconds thereafter until each patient reported analgesia. The onset of analgesia was defined as the loss of painful sensation to pinprick measured from the time of administration of the initial test dose. This study was done in a double blinded fashion. Statistical analysis was done using one way analysis of variance and the Tukey and Duncan's multiple range tests. Statistical analysis of the physical properties of the two study solutions was done with the student's t test. Significance is $p < 0.05$.

Results. The maternal characteristics did not differ among the groups. The pH and pCO_2 differed significantly between the buffered and nonbuffered groups (Table 1). A statistically significant difference in the onset of analgesia in the pH adjusted groups was noted (Table 2). Position had no effect on the onset of analgesia.

Table 1. Characteristics of the study solutions.

	pH	Specific Gravity	pCO_2 (torr)
2CP	4.38±0.01*	1.338±0.00	18.4±2.17*
Buffered 2CP	7.7 ±0.04	1.339±0.00	114.9±3.03

Values are mean ± SD. *$p < 0.05$.

Table 2. Comparison between 2% 2CP and buffered 2CP.

Group	Onset (min)	Duration (min)
I	4 ± 1.15	26.2 ± 6.09
II	2.6 ± 0.85*	27 ± 4.24
III	4.3 ± 1.01	26.7 ± 1.17
IV	2.7 ± 0.63*	26.5 ± 1.58

Values are mean ± SD. *$p < 0.05$.

Discussion. The pH adjustment of 2% 2CP to 7.7 with $NaHCO_3$ significantly accelerated the onset of action when administered epidurally. Position had no effect on the onset of action. This data is clinically relevant in labor patients who must not assume the supine position. The duration of action was not significantly different in any group.

References

1. Douglas MJ, McMorland GH, Jeffery WK, Kim JHK, Ross PL, Gambling DR, Swenerton JD, Azelson JE: The effect of pH adjustment on epidural anesthesia for cesarean section. Anesthesiology 65:A380, 1986.
2. DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RA: Comparison of pH adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 65:760-764, 1986.

Title: THE EFFICACY OF GLUCOSE TEST STRIPS TO DETECT DURAL PUNCTURE DURING CONTINUOUS EPIDURAL ANALGESIA

Authors: W.E. Ackerman, M.D., M.M. Juneja, M.D., D.M. Kaczorowski, D.O.

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Introduction. Various methods have been described to distinguish CSF from local anesthetics (1,2). However, one cannot consistently aspirate free flowing fluid from an epidural catheter. When only a small volume of aspirate is obtained, 0.3 ml of the aspirate will contain local anesthetic injectate as this is the volume of most 20g epidural catheters. The purpose of this study was to compare the efficacy of thiopental and the pH, protein and glucose zones of urine test strips in detecting CSF mixed with saline or local anesthetics in dilutions of 1:1, 1:10 and 1:20 (CSF:local anesthetic).

Methods. After Institutional Review Board approval, CSF was collected from discarded 4 quadrant aspirates from 15 fasting patients who had requested SAB for their surgeries and who had normal measured plasma glucose levels and were receiving IV fluids without glucose. The CSF was mixed in separate test tubes with local (with and without epinephrine) and with saline to make dilutions of 1:1, 1:10, and 1:20 (CSF:local anesthetic or saline). Using a micropipette, 0.05 ml of study solution was placed on either the pH, protein and glucose zones of the Chemstrip-9^{R}, urine test strips or 0.5 ml were added to 0.5 ml of thiopental. Each test was done five times and was read by an independent blinded observer to standardize time. Observers were instructed to look for a color change on the test strip and a precipitate with thiopental.

Results. Thiopental resulted in a precipitate with plain local anesthetic and all of the CSF:local anesthetic dilutions. The protein zones reacted falsely positive with each of the local anesthetics. The pH zones were effective in detecting CSF:local anesthetics to a dilution of 1:1 (Table 1). The glucose test strips were effective in detecting CSF local anesthetic mixtures to a dilution of 1:20 (Table 2). The addition of epinephrine had no effect on any of the test results. Statistical analysis was done using the complex Chi squared test. Significance is $p < 0.05$.

Discussion. The thiopental and protein zone tests were not useful in detecting CSF diluted with local anesthetics. The pH test zones were effective in detecting CSF:local anesthetics only at a dilution of 1:1 (Table 2). The glucose test zone was the most accurate test for detecting small amounts of CSF diluted with saline or local anesthetics. The glucose zone tests would be useful in detecting CSF diluted with local anesthetics or saline from catheters during continuous epidural analgesia.

Table 1. Incidence of positive responses on pH test zones (change in color) (each test dose 5 times).

Dilution	Plain	1:1	1:10	1:20
CSF	5	—	—	—
Epinephrine	0	—	—	—
Saline	0	—	—	—
Bupivacaine				
0.5%	0	5*	0	0
0.25%	0	5*	0	0
Lidocaine				
2%	0	5*	0	0
1%	0	5*	0	0
2-chloroprocaine				
3%	0	5*	0	0
2%	0	5*	0	0

*$p < 0.05$.

Table 2. Incidence of positive responses on glucose test zone (change in color) (each test done 10 times).

Dilution	Plain	1:1	1:10	1:20
CSF	5	—	—	—
Epinephrine	0	—	—	—
Saline	0	—	—	—
Bupivacaine				
0.5%	0	5	5	5
0.25%	0	5	5	5
Lidocaine				
2%	0	5	5	5
1%	0	5	5	5
2-chloroprocaine				
3%	0	5	5	5
2%	0	5	5	5

The addition of 1/200,000 epinephrine to the local anesthetic solutions had no effect on the results.

References

1. Reisner LS: Epidural test solution or spinal fluid? Anesthesiology 14:451, 1976.
2. Catterberg T: Local anesthetic versus spinal fluid. Anesthesiology 46:309, 1977.

Title: **TROMETHAMINE PROLONGED THE ONSET AND DURATION OF ANALGESIA OF EPIDURAL 2-CHLOROPROCAINE**

Authors: W.E. Ackerman, M.D., M.M. Juneja, M.D., D.M. Kaczorowski, D.O., D. Denson, Ph.D.

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Introduction. Increasing the pH of local anesthetics has been reported to hasten the onset of epidural anesthesia (1,2). The purpose of this randomized double-blinded study is to compare the onset of epidural anesthesia comparing two buffers to increase the pH of 2% 2-chloroprocaine (2CP).

Methods. Institutional Review Board and informed consent were obtained from 40 healthy parturients who had requested epidural analgesia for labor. The epidural catheters were placed at the L2-3 or L3-4 interspaces and were advanced 2-3 cm. All epidural catheter placements were done using a loss of resistance technique using air and with the patient in a sitting position. The patients were randomly assigned to one of four groups of ten patients. Group I received 2% 2CP buffered to a pH of 7.1 with sodium bicarbonate. Group II received 2CP buffered to a pH of 7.1 with tromethamine. Group III received 2CP buffered to a pH of 7.7 with sodium bicarbonate. Group IV received 2CP buffered to a pH of 7.7 with tromethamine. Three (3) ml of study solution were administered through the catheter as a test dose followed by a latency period of two minutes. Subsequently, 5 ml of epidural study solution were administered.. The posterior S2-3 dermatomes were tested for analgesia to pinprick at time 0 and every 30 seconds thereafter until each patient reported analgesia. The onset of analgesia was defined as the loss of painful sensation to pinprick measured from the time of administration of the initial test does. This study was done in a double blinded fashion. Statistical analysis was done using the one-way analysis of variance and the Tukey and duncan's multiple range tests. Statistical significance is $p < 0.05$.

Results. The maternal characteristics did not differ among the groups. A statistically significant difference in the onset and the duration of analgesia was noted in both of the tromethamine buffered groups when compared to the bicarbonate buffered groups (Table 1).

Table 1. Comparison between sodium bicarbonate buffered 2CF with tromethamine buffered 2CP

	Group I	Group II	Group III	Group IV
Onset of analgesia (min)	4.45 ±0.77	5.6 ±0.99	2.65 ±0.85*	5.4 ±0.39
Duration of analgesia (min)	29.5 ±6.6*	59.1 ±10.39	26.2 ±4.24*	55.7 ±4.5

Values are mean ± SD.
*$p < 0.05$.

Discussion. The pH adjustment of 2% 2CP to 7.7 with $NaHCO_3$ significantly accelerated the onset of analgesia when compared to tromethamine. The pH adjustment of 2% 2CP with tromethamine prolonged both the onset and duration of analgesia when compared to the $NAHCO_3$ treated groups. We conclude that factors other than pH alone are responsible for the more rapid onset of analgesia of 2% 2CP buffered to a pH of 7.7 with $NaHCO_3$.

References:

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2. DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RP: Comparison of pH adjusted lidocaine solutions for epidural anesthesia. Anesth Analg 65:760-764, 1986.

Title : COMPARISON OF DIAZEPAM TO LORAZEPAM AS AN ADJUVANT TO FENTANYL ANESTHESIA FOR CABG

Authors : A Aggarwal, M.D., AC Reynolds, M.D., T Olund, M.D., JJ Entress, M.D. and MS Dhamee, M.D.
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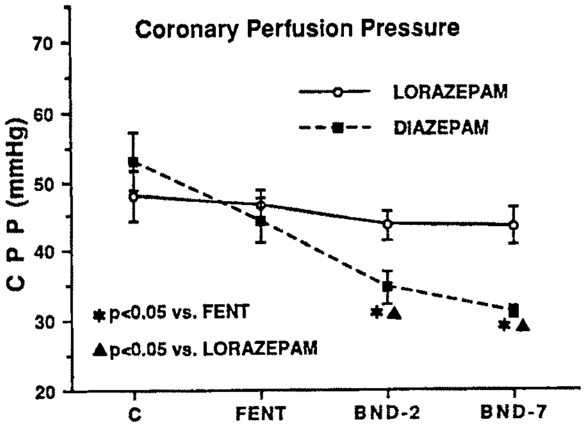
INTRODUCTION. High dose fentanyl has achieved widespread acceptance as an anesthetic for myocardial revascularization. To prevent intraoperative awareness, benzodiazepines are often used as adjuncts. The use of diazepam with fentanyl has been reported to cause a decrease in cardiac output, systemic vascular resistance and depression of myocardial contractility,[1] while use of lorazepam with fentanyl has been shown to cause a decrease in systemic vascular resistance and left ventricular stroke work index.[2] This double blind, randomized, prospective study of patients undergoing elective myocardial revascularization was undertaken to compare directly the hemodynamic effects of these two drugs in combination with fentanyl.

METHODS. After institutional approval, informed consent was obtained from 15 patients undergoing anesthesia for elective CABG. Exclusion criteria included ejection fraction <35% and preoperative chronic benzodiazepine therapy. All patients were premedicated with morphine 0.15 mg/kg and scopolamine 6 ug/kg (maximum of 0.5 mg), 1/2-1 hour pre-op. Patients were randomized into two treatment groups. After a standard fluid pre-load of 10 cc/kg of normal saline, both groups received fentanyl citrate infusion, at a rate of 500 ug/min for induction of anesthesia, to a maximum of 75 ug/kg. The end point of narcotic administration was clinically determined by the anesthesiologist in each case. Concurrently, patients also received vecuronium bromide 0.15 mg/kg. Patients in one treatment group then received lorazepam 0.06 mg/kg and in the other group diazepam 0.24 mg/kg (equipotent doses)[3] over a two minute period. Patients were ventilated with oxygen by mask to maintain a normal $ETCO_2$. No intervention which could alter hemodynamic variables, including endotracheal intubation, was allowed during the study period. Hemodynamic parameters were measured: 1) preinduction (C); 2) two minutes after completion of fentanyl infusion (FENT); 3) two minutes after benzodiazepine administration (BND-2); and 4) seven minutes after benzodiazepine administration (BND-7). Hemodynamic measurements and observations included: heart rate, systemic arterial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, right atrial pressure, thermodilution cardiac output, diagnostic ECG leads II and V. Calculated indices included cardiac index, stroke index, coronary perfusion pressure, left ventricular stroke work index and right ventricular stroke work index. Data analysis consisted of two way ANOVA with repeated measures followed by Fisher's LSD.

RESULTS. The two groups were demographically similar with regard to age, sex, pre-op cardiac medications and left ventricular function. All hemodynamic parameters were similar in the two groups for preinduction and postnarcotic infusion periods. Coronary perfusion pressure (CPP) calculated as diastolic blood pressure minus pulmonary artery wedge pressure, decreased significantly following diazepam administration ($P<0.05$), while it was unchanged in the lorazepam group (fig. 1). Cardiac index and left ventricular stroke work index also decreased significantly from postnarcotic control values following diazepam administration ($P<0.05$). There were no significant changes in these indices in the group receiving lorazepam. Mean arterial pressure decreased following benzodiazepine administration in both groups but was significantly greater for patients receiving diazepam. There were no significant changes in systemic vascular resistance or stroke index in either group.

DISCUSSION. This double blind, randomized, prospective study reveals that the combination of diazepam with fentanyl leads to decreases in coronary perfusion pressure, cardiac index and left ventricular stroke work index as compared to lorazepam with fentanyl. Since a decrease in coronary perfusion pressure in this group of patients with significant coronary artery disease may lead to myocardial ischemia, we conclude that lorazepam is a better choice as an adjuvant to fentanyl anesthesia.

Figure 1



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TITLE: THE EFFECTS OF ISOFLURANE ON CEREBRAL BLOOD FLOW AUTOREGULATION DURING HYPOTHERMIC CARDIOPULMONARY BYPASS

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INTRODUCTION. Cerebral blood flow (CBF) autoregulation is conceptionally viewed in terms of either pressure-flow (constant CBF over a range of blood pressure) or metabolism-flow (CBF changes as cerebral oxygen consumption changes). Pressure-flow cerebral autoregulation is maintained during cardiopulmonary bypass (CPB) with fentanyl anesthesia.[1] It has been suggested that metabolic autoregulation may be disrupted by isoflurane during CPB,[2] but there has been no systematic study of pressure-flow autoregulation during CPB with isoflurane anesthesia.

METHODS: Following approval by IRB and informed consent 21 patients who were scheduled to undergo hypothermic CPB were randomly assigned to receive one of three different doses of isoflurane during CPB. Group I (n=7) received 0%, Group II (n=7) 0.6%, and Group III (n=7) 1.2% isoflurane. Anesthesia was induced and maintained with midazolam, fentanyl, and vecuronium. To maintain constant blood levels of the intravenous anesthetic drugs during determinations of CBF, fentanyl and midazolam were administered by a pharmacokinetic model-driven drug infusion system that kept fentanyl and midazolam at plasma levels of 2 ng/ml and 50 ng/ml, respectively.

CBF was measured using xenon^{133} clearance methodology.[3] Two extracranial gamma emission detectors were placed over the right and left temporal lobes and the average values from both sites used to determine CBF. CBF determinations were made at hypothermic conditions with nasopharyngeal temperature 27° C and pump flow of 1.6 L/min/m^2. Blood gas management was directed at maintaining PCO_2 of 40 mm Hg (range 35 - 41) and PO_2 of < 250 mm Hg (range 100 - 287) which were not corrected for temperature. After obtaining the above conditions the first CBF measurement was completed (A). Mean arterial pressure was then raised ≥ 20% by bolus administrations of phenylephrine and the second CBF measurement made (B).

RESULTS: The results of mean ± SD and range of CBF (ml/100g/min), MAP (mmHg), PCO_2 (mmHg), and nasopharyngeal temperature (°C) are tabulated for each group at measurement points A and B.

	A	B
CBF		
Group I	23 ± 6 (15-34)*	24 ± 5 (17-32)*
Group II	14 ± 7 (4-22)	13 ± 5 (5-19)
Group III	15 ± 9 (12-22)	16 ± 5 (10-22)
MAP		
Group I	62 ± 16 (38-83)*	80 ± 21 (46-108)*
Group II	32 ± 10 (22-46)	40 ± 13 (30-58)
Group III	35 ± 9 (23-50)	47 ± 14 (33-71)
PCO_2		
Group I	36 ± 1 (35-39)	36 ± 1 (35-39)
Group II	39 ± 2 (36-41)	38 ± 2 (36-40)
Group III	36 ± 2 (32-39)	36 ± 2 (34-39)
TEMP		
Group I	28 ± .4 (27-28)	27 ± .6 (26-28)
Group II	27 ± 1 (26-28)	27 ± 6 (26-28)
Group III	27 ± 1.4(24-28)	27 ± .1 (25-28)

*p < .02 Group I vs Groups II and III

The CBF-MAP slope was computed as the ratio of the change in CBF divided by the changes in MAP from A to B. The slopes (normal range) were Group I = .13 (- .15 to .58), Group II = -.16 (-1.49 to .69) and Group III = .08 (-.14 to .43). No mean slopes were different from 0 nor were there any significant differences among groups.

DISCUSSION: These data demonstrate that CBF pressure-flow autoregulation during hypothermic CPB is maintained when isoflurane is used during CPB in doses of 0.6% and 1.2%. Although isoflurane reduced CBF as reported before[2], it did not abolish pressure-flow autoregulation over the range of pressures studied (22-71 mm Hg). The reduction in CBF with isoflurane is a result of further reduction in cerebral metabolism.[2] Intuitively the attenuation of the stress response to CPB should be beneficial and isoflurane has been shown to prevent this stress response.[4] Knowledge that autoregulation is maintained when isoflurane is used during CPB is reassuring since it is a useful adjunct to opioid anesthesia during CPB and commonly used to lower the perfusion pressure. Changing the perfusion pressure during isoflurane anesthesia does not alter CBF over the commonly encountered ranges (21 - 71 mm Hg) while on cardiopulmonary bypass.

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Title: KETAMINE HYDROCHLORIDE (KH) FAILS TO PROTECT AGAINST ACUTE GLOBAL HYPOXIA IN THE RAT

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Introduction: During the past decade, a number of reports have indicated that KH has neuroprotective properties. This is based on studies demonstrating KH can attenuate hemispheric ischemia in the gerbil, antagonize the action of excitatory amino acids in the CNS by blocking the n-methyl-d-aspartate(NMDA) receptors and inhibiting glutamate-induced intracellular calcium influx; and accelerating the postischemic restoration of high-energy phosphates in brain.However, information appears to be lacking as to whether KH can enhance functional survival after an insult such as acute global hypoxia. This is important because it has been demonstrated that KH increases CBF, $CMRO_2$ and can cause increased ICP even in the face of normal CSF pathways. In order to evaluate this paradox, we studied survival rates in animals rendered hypoxic by low O_2 tensions and tested their posthypoxic behavior comparing placebo control against KH in dossing equipotent to that used in clinical practice.

Methods: Sprague-Dawley rats, each weighing 350-500 grams and having free access to tap water and food pellets were studied. Initially, two groups of 5 animals each were given either placebo or intraperitoneal KH, 40mg/kg and placed in pairs in a gas tight flow-through chamber containing 3.70% O_2 and 96.30% N_2 piped in at a rate of 34 l/min. The chamber was warmed by a heating unit and the temperature within the box maintained between 31-33°C. The gas mixture was continuously sampled by a mass spectrometer, oxygen analyzer, and discontinuously monitored by injecting air samples obtained from the flow-through chamber using a polargraphic electrode. The survival time was calculated from time of decrease in the O_2 concentration to 3.70% until the cessation of spontaneous respiration or terminal gasp. Rectal temperatures were taken immediately after terminal gasp or cessation of respiration and the survival times were analyzed using the Student t test. A second group of 8 rats were maze trained prior to hypoxia so that their individual maze runs varied by no more than 10% of the average of 10 trials. The maze trained rats were divided into 2 groups of 4 each and placed inside the gas chamber with one group receiving a 40mg/kg intraperitoneal dose of KH and the other group (control) an equivalent volume of saline. The duration of hypoxia was shortened to 55 seconds less than the shortest survival time from the previous experimental group. The rats were then permitted to recover and after 24 hours were given 10 trial runs each in the maze with the average run time and number of errors calculated. Data was compared between control and KH pretreatment groups using the Student t test. This study was approved by the Animal Care Committee, University of Texas Health Science Center in San Antonio.

Results: As can be noted in Table 1, survival time was considerably shortened in the KH group when compared to control, with p=<0.05.

Table 1. Survival Times

Control±SEM(N=5)	KH±SEM(N=5)
26.3±1.9 min.	14.5±1.3 min

p=<0.05

Of the eight maze-trained animals, four were assigned to the Control Group and four to the KH Group and all exposed to the hypoxic mixture of 3.70% O_2 and 96.30% for a period of eight minutes. Table 2 indicates a significant difference in maze running in both the Control (p=<0.05) and KH (p=<0.05) groups when comparing the prehypoxic and posthypoxic epochs. There were no significant differences when comparing prehypoxic maze running of Control against KH, nor was there any statistical difference in maze running time between Control and KH in the posthypoxic epochs.

Table 2. Maze Run Times
(8.0 min hypoxia)

Control±SEM		KH±SEM	
prehypoxia	posthypoxia	prehypoxia	posthypoxia
13/1±1.5 sec	19.2±1.s sec	9.7±0.6 sec	20.3±1.6 sec

NS
p=<0.05 p=<0.05
NS

Total errors were similar in both groups for maze running. We were using a T-shaped maze with the rats conditioned to turn to the left. In the prehypoxic period, all animals were trained to a zero (0) indecision level. In the posthypoxic epoch, the 8 controls manifested indecision on left turning ability 6 times, while the 8 KH animals were indecisive on 16 occasions during the 10 trial runs.

Discussion: It appears that KH has a multiplicity of effects depending on the receptor sites or target organs involved. In terms of its anesthetic component, KH increases circulating catecholamines, CBF, $CMRO_2$, ICP, blood pressure and heart rate. Its analgesic effects relates to the ability of KH to interact with opiate receptors and it has been used to provide epidural and subarachnoid analgesia. Our data suggests that KH provided the initial insult by decreasing intracranial compliance, with the additive effect of hypoxia and probable accompanying hypercarbia increasing ICP and producing ischemia, brainstem compression of cardiopulmonary centers, herniation and death. That the short (8.0 min) period of hypoxia had a marked effect on behavioral dynamics can be seen by the slow scores of the Control and KH posthypoxic animals in running the maze. Thus it appears that in the rat hypoxia model, KH makes the CNS more vulnerable to hypoxia. Perhaps the ability of KH to successfully block the NMDA receptors without effecting intracranial compliance depends on using a much lower concentration, or using pretreatment with another compound having pharmacological qualities that would decrease $CMRO_2$, CBF and ICP.

Title: AN ALTERNATE OXYGEN DELIVERY SYSTEM TO INFANTS AND CHILDREN IN THE POST ANESTHESIA CARE UNIT

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Introduction. Hypoxemia following general anesthesia in infants and children has been well documented (1). Our practice of administering supplemental humidified oxygen to these patients in the PACU has been with a hose and tape method (see Fig. 1). This study was designed to compare the rate of rejection of O_2 supplement and level of arterial oxygen saturation (SaO_2) in patients receiving oxygen by mask or by the proposed method.

Methods. Following institutional review board approval and parental informed consent, 66 ASA I-III patients (2 mo-6 yrs of age, mean 2.3) scheduled for surgery under general anesthesia were randomly allocated to receive O_2 by mask or by the proposed method. Patients were further stratified into low and high risk groups for developing postoperative hypoxemia. The latter group included patients with coexisting lower and upper respiratory tract disorders, history of prematurity, anemia and cardiac disease. Patients who were intubated or had a tracheostomy tube in place, or patients requiring nebulized medications in the recovery room or premature infants requiring a head box were excluded from the study. The choice of premedication or anesthetic technique was not restricted. SaO_2 measurements were obtained in the following sequence: induction (FiO_2 0.3), postanesthetic (RA), arrival in PACU (RA 3 min) and at 5, 15 and 30 min following O_2 supplementation. With both methods of delivery, the O_2 was humidified and an FiO_2 of 0.4 given at 6-8 lit/min to children < 2 yr and at 8-10 lit/min to children 2-6 yr. If the mask was rejected following two attempts, the patient was switched to the proposed method, and the study completed. The presence or absence of rejection of O_2 supplementation source by the child was recorded by the PACU nurse. SaO_2 measurements were obtained using the Nellcor® 200 model with ECG synchronization in the PACU. The data were analyzed with Fisher's exact test. All tests performed were two-tailed at $\alpha = .05$.

Results. The rate of rejection of the mask within the first 5 min in PACU was 81.0% in the low risk group and 81.8% in the high risk group, while no patient rejected the hose in either group. A summary of the data on SaO_2 measurements is presented in Tables 1-2. The preoperative induction SaO_2 and the end of surgery SaO_2 measurements were not statistically different among all four groups. The incidence of hypoxemia ($SaO_2 < 90\%$) upon arrival to the PACU was statistically significant $p < .05$ for the high risk group 4/20 (20%), when compared with the low risk group 1/46 (2.1%). The improvements in SaO_2's following administration of O_2 with the hose were statistically significant $p < .05$ for both the low and high risk groups (Table 2).

Discussion. The results of this study show that the conventional mask is rejected by > 80% of infants and children in the immediate postoperative period. In addition to provoking crying and anxiety the mask may cause trauma to the eyes. We have also confirmed prospectively that the group at high risk for developing hypoxemia includes patients with coexisting disease (respiratory, cardiac, anemia and prematurity) (2). The improvement in SaO_2 from room air with the hose was also significant in both low and high risk patients. Based on our experience we recommend this method as being more comfortable while providing adequate O_2 supplementation to infants and children recovering from general anesthesia.

Table 1. SaO_2 in PACU (Hose Only)*

Time	Risk	n	Mean±S.D.	Range
1) RA (3 min)	low	42	97.4±2.2	(91-100)
	high	18	93.4±7.6	(68-100)
2) O_2 + 5 min	low	42	99.5±0.9	(96-100)
	high	18	99.3±1.0	(96-100)
3) O_2 + 15 min	low	42	99.5±0.8	(97-100)
	high	18	98.9±1.9	(92-100)
4) O_2 + 30 min	low	41	99.4±0.9	(96-100)
	high	18	99.3±0.8	(98-100)

Table 2. Changes in SaO_2 (T_2-T_1) following 5 min of O_2 supplement (Hose only)*

Risk	n	Mean ± S.D.	Range	p Value
Low	42	2.1±1.8	-1 to 7	p < .05
High	18	5.9±6.8	0 to 28	p < .05

*Mask sample size inadequate for analysis.

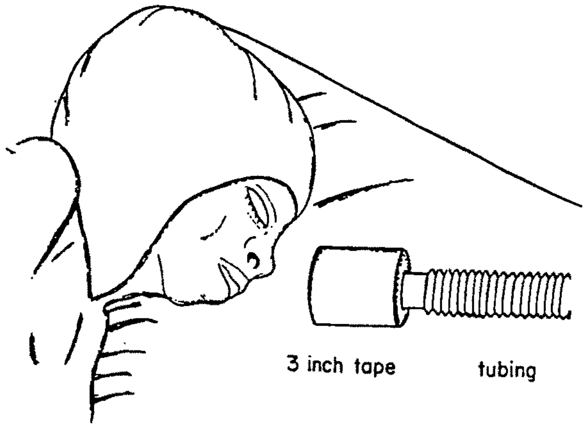

Figure 1

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Title: EFFECTS OF METRONIDAZOLE ON NEUROMUSCULAR TRANSMISSION IN RABBITS

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Introduction. Several antibiotics have been shown to effect neuromuscular function (1). Metronidazole (Met) is an antibacterial agent which has been reported to cause acute and chronic neurologic toxicity (2,3), however its effects on neuromuscular transmission have not been previously described. This study was undertaken to investigate the possible effects of metronidazole on neuromuscular function.

Methods. After approval of the Animal Investigation Committee, New Zealand albino rabbits (N=25) were anesthetized with intravenous pentobarbital, tracheostomized, and a carotid artery cannulated. Mechanical ventilation was instituted to maintain arterial blood gas values of $PaO_2 > 200$ torr, $PaCO_2 = 40 \pm 5$ torr, and a $pH = 7.40 \pm 0.05$. Following a previously described model (4), a sciatic nerve was ligated and supramaximally stimulated. The twitch responses of the ipsilateral hind limb plantar flexors were continuosly recorded via a Grass FT10C force-displacement transducer and Beckman dynagraph. After at least 5 min of stable recorded twitch tensions, drug(s) were administered IV as follows in groups of five animals each:

Group #1- Met 50mg/kg
Group #2- Vecuronium (Vec) infusion (mean twitch decrement 58± 3%), then Met 25mg/kg
Group #3- Succinylcholine (Sux) infusion (mean twitch decrement 51± 2%), then Met 50mg/kg
Group #4- Dantrolene 0.2mg/kg, then Met 50mg/kg
Group #5- Sux 0.1mg/kg bolus, then 30min later Met 50mg/kg and repeat Sux bolus 0.1mg/kg

In groups #1-4 twitch tensions were measured, and in group #5 time to 75% twitch tension recovery was recorded. Each animal served as its own control (i.e. prior to Met dosing), and data were analyzed as percent of control using the paired t-test with differences considered significant at a p-value of 0.05.

Results. Metronidazole alone and in the presence of vecuronium significantly increased twitch tension. Dantrolene blocked this effect of metronidazole. Metronidazole did not prolong the action of a succinylcholine bolus, but potentiated the block of a succinylcholine infusion.

Discussion. In this study metronidazole facilitated neuromuscular transmission, and reversed the blockade of a vecuronium infusion. This appeared to occur mainly via an enhancement of calcium's action in skeletal muscle contraction, as a low dose of dantrolene (a calcium channel blocker in skeletal muscle) prevented metronidazole's augmentation of twitch tension. Metronidazole did not appear to inhibit pseudocholinesterase to any significant degree since it did not prolong the action of a succinylcholine bolus. Interestingly, metronidazole enhanced the depolarizing block of succinylcholine while partially reversing the nondepolarizing competitive block of vecuronium. Postulating an agonist effect of metronidazole at the cholinergic skeletal muscle receptor would explain these findings. While these theories would certainly require further investigations to support, it is apparent from this study that metronidazole does not exhibit the same neuromuscular blocking effects as the '-mycin' group of antibiotics (1).

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TABLE

Group #	Drug(s)	%Δ Twitch Tension
1	Met	+ 43.2 ± 8.9 (*)
2	Vec infusion + Met	+ 102 ± 6.7 (*)
3	Sux infusion + Met	- 22.6 ± 7.6 (*)
4	Dantrolene + Met	- 0.4 ± 2.6
		%Δ75% Recov Time
5	Sux bolus vs Met + Sux bolus	- 1.6 ± 11.8

All results recorded as Mean ± S.E.M. ; (*)= $p < 0.05$

TITLE: SINGLE BLIND COMPARISON OF CONTINUOUS EPIDURAL CLONIDINE, EPIDURAL MORPHINE, AND PARENTERAL NARCOTIC ANALGESIA UPON POST ABDOMINAL SURGERY NEUROENDOCRINE STRESS RESPONSE (CORTISOL)

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INTRODUCTION: Epidural narcotic analgesia has been shown to have a modest effect in combination with regional anesthesia upon the neuroendocrine response to major abdominal surgery and related post operative stress(1). We sought to assess whether the alpha$_2$ adrenergic analgesia associated with intraspinal clonidine would yield a reduced neurondocrine response to abdominal surgery (2).

METHODS: A group of major abdominal surgical patients were divided into three groups for post operative analgesia: Group 1 (n=5) received 150 mcg bolus dose of epidural clonidine (C), followed by a 24 hr. continuous epidural clonidine HCI infusion, 25-50 mcg per hour; Group 2 received 3-5 mg bolus doses of epidural morphine (M) q 8-12 hours titrated to achieve satisfactory analgesia, and Group 3 received conventional parenteral narcotic analgesia (GA). All patients were similarly premedicated. All patients in Groups 1 and 2 had a low thoracic or high lumbar epidural catheter placed and tested with local anesthetics prior to combined epidural general endotracheal anesthesia induction; Group 3 patients received either a fentanyl based high dose narcotic anesthetic or a fentanyl based balanced anesthetic technique. A baseline preinduction serum cortisol was obtained along with determinations at 8 and 24 hours postop respectively. All clonidine patients were allowed access to morphine delivered by an Abbott PCA delivery system, while Group 3 patients received morphine as 1-2 mg intravenous boluses for 24 hours titrated to achieve satisfactory analgesia. All patients gave both written and oral informed consent, and the studies were approved by the Dartmouth Hitchcock Medical Center's IRB.

RESULTS: The results are shown in Table 1.

TABLE I
CORTISOL (mean ± S.E.)

Group (n)	Baseline	3 Hr(Baseline-8 Hr)	24 Hr(Baseline-24 Hr)
1. C (5)	10.1±2.0	14.7± 3.2†† (1.8± 1.8)††	14.7±1.6†† (4.6± 2.0)
2. M (11)	11.1±1.1	26.8±3.7** (15.7±3.1)	21.8±3.5** (10.7±3.1)
3. G A (16)	17.6±3.0	38.1±3.8 (23.4±3.90)	34.6±3.6 (17.1±3.6)

Statistics: Anova/Kruskal-Wallis/Fisher's test:
Between sampling times (Baseline vs 8/24 hr)
*= p 0.01 & †=p<0.05, between groups (1,2,3)
**=p<0.05, ††=p<0.01.

Baseline cortisol was not significantly different among the groups though, inexplicably, Group 3 had an elevated mean. Group 3 patients (general anesthesia only) demonstrated significant increases in serum cortisol at both 8 and 24 hours following surgery. The cortisol response to stress in Group 2 patients (epidural MS) was significantly reduced compared to conventional parenteral analgesia (Group 3) as noted by others in the past. Similarly, Group 1 patients had a much reduced early and late rise in cortisol compared to the parenteral analgesics (p< 0.01). Most interesting, clonidine treated patients had a lesser mean numerical increase in cortisol at 8 and 24 hours than epidural morphine treated patients.

DISCUSSION: Previous studies have shown that stress associated with major surgery can be modified to some extent by the use of regional epidural anesthesia intraoperatively, and that this effect is sustained to some extent by the use of post operative epidural morphine (1). We reasoned that the pronounced stress inhibition seen with local anesthetics given epidurally might be better sustained by using an epidural analgesic such as clonidine with its ability to block alpha adrenergic outflow at several levels of the neuraxis. Furthermore, no motor block is seen with these doses of epidural clonidine (up to 50 mcg/hr.). Though preliminary, this technique appears to provide a more profound blockade of cortisol release than epidural morphine as used in this study. Further work is proceeding including analysis of the plasma clonidine levels obtained at the time of cortisol sampling.

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Title: The EEG Effects of Pentamorphone in the Dog

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Introduction: Pentamorphone (Anaquest) is a new potent opioid currently undergoing clinical trials for its use as an analgesic. It is reported to be six times as potent as fentanyl with a ten-fold higher therapeutic index. Initial animal studies reveal pentamorphone has less cardiovascular side effects and respiratory depression than fentanyl. This study was completed to evaluate the EEG effects of pentamorphone as compared to equipotent doses of fentanyl when given as the sole anesthetic in the dog.

Methods: The study was reviewed and approved by the Institutional Animal Care and Use Committee. Seven dose levels, comparable in terms of general anesthetic potency, based on existing information, were tested. Anesthetic pentamorphone dose levels evaluated were 12.5, 25, 75, 125, 250, 375, and 500 ug/kg. Comparable doses of fentanyl studied were 75, 150, 450, 750, 1500, 2250, and 3000 ug/kg. Forty-two healthy, untrained, unpretreated mongrel dogs were randomly assigned to a test drug and dose level. Three dogs at each dose level were studied. On arrival to the laboratory, an intravenous line was placed and the dog was given succinylcholine, 1 mg/kg IV. The dog was intubated and mechanically ventilated on 100% oxygen to maintain an arterial PCO_2 between 35 and 45 mmHg as confirmed by an arterial blood gas analysis.

A needle EEG electrode was then placed in each scalp quadrant and referred to one at the midpoint between them. Pre-amplifiers were set at 1 and 100 Hz for 1/2 amplitude attenuation. Raw EEG was monitored by 4 channel on-line printout and subjected to a Fast Fourier Transformation for each 4 second EEG segment. Its power spectra were also displayed on-line as Compressed Spectral Array (CSA, Biologic Systems Corp). Both raw and spectral EEG data were stored for off-line review.

Baseline EEG recordings were made for 60 seconds after placement of the leads and the dog was then given a bolus of the test drug intravenously(total elapsed time from administration of succinylcholine and intubation was approximately 3 minutes). EEG monitoring was continued for at least 15 minutes following test drug injection, after which the dog was sacrificed.

EEG data were visually analyzed by a neurologist experienced in EEG interpretation blinded to the drug and drug dose given.

Results: Visual analysis of the EEG data revealed electrographic seizure discharges caused by both pentamorphone and fentanyl. EEG effects of the drugs were classified on the basis of 4 distinct patterns of CSA data.

PATTERN I (non-specific anesthetic effects). This patterns was characterized by enhancement of slow EEG waves occurring about 30 seconds after injection. Little or no spectral change in the higher EEG frequencies occurred. This was the only pattern seen at pentamorphone doses of 75 ug/kg and below and at fentanyl doses of 450 ug/kg and below. It was also seen in 50% of the dogs receiving higher fentanyl doses.

PATTERN II (immediate seizure onset). This pattern is characterized by electrographic seizure activity occurring within 30 seconds of drug administration. The electrographic seizure varied in duration between 30 seconds and 3 minutes, terminated by an abrupt global EEG attenuation. Slow wave predominance returned gradually thereafter. This pattern was seen in 80% of the dogs given pentamorphone at doses of 125 ug/kg or higher and 25% of the dogs receiving fentanyl in doses of 750 ug/kg or higher. The duration of the electrographic seizure was shorter in the dogs receiving fentanyl.

PATTERN III (delayed seizure onset). This pattern was characterized by electrographic seizure discharges occurring later than one minute after injection of the test drug. This pattern was seen in 25% of the dogs receiving fentanyl at doses of 750 ug/kg and above.

PATTERN IV (multiple seizure activity). this pattern was characterized by electrographic seizure discharges occurring both within 30 seconds of injection and later than one minute after injection of the study drug. This pattern occurred in 20% of the dogs in the pentamorphone group at doses of 125 ug/kg and above. No dog receiving fentanyl experienced multiple seizures.

Discussion: Pentamorphone and fentanyl differed appreciably in their EEG effects in the dog when compared by the occurrence of electrographic seizures at comparable anesthetic dose levels. The electrographic seizure threshold level was at comparable anesthetic dose levels, 75 and 125 ug/kg for pentamorphone and 450 and 750 ug/kg for fentanyl. However, fentanyl was less epileptogenic; only 50% of the dogs receiving fentanyl experienced electrographic seizures in comparison to 100% of the dogs receiving pentamorphone at doses above the seizure threshold.

The temporal profile of the EEG effects differed between the two drugs. Electrographic seizure activity was of immediate onset in the dogs receiving pentamorphone, while 50% of the dogs who received fentanyl and experienced electrographic seizure activity had delayed onset. In addition, multiple seizures were only seen in dogs receiving pentamorphone.

The clinical correlation of seizure activity differs between the two drugs as well. In previous studies at this institution evaluating pentamorphone and fentanyl as the sole anesthetic in dogs, tonic-clonic jerking compatible with generalized seizure activity was frequently seen in dogs given pentamorphone in doses of 125 ug/kg and up while no such activity was seen with fentanyl doses up to 3 mg/kg.

Title: INTERCOSTAL NERVE BLOCK FOR MINOR BREAST SURGERY

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Introduction. Intercostal nerve block (ICNB) is rarely used as an alternative to general anesthesia (GA) for minor breast surgery (1). The block is associated with high blood levels of local anesthetics which can be lowered approximately 25% by the addition of vasoconstrictors (2). This study was designed to compare ICNB with GA for breast surgery with respect to efficacy, surgical stress and postoperative analgesia, further to evaluate epinephrine and ornipressinum (POR 8®, Sandoz) as vasoconstrictors in the local anesthetic solution.

Methods. With institutional approval, informed consent was obtained from a total of 45 female patients (ASA class I and II) from 23 to 80 years of age (mean 45 years). They where scheduled for elective biopsy of breast tumors and premedicated with midazolam per os. The patients were randomly allocated into three groups. In group A (n=15) ICNB was performed with lidocaine 2% and epinephrine 1:200 000 (Xylocain®, Astra). In group B (n=15) ornipressinum 0.2U/ml was added to the lidocaine solution instead. Patients of these groups were placed in the lateral decubitus position. Five segments ranging from T3 to T7 were blocked with 5 ml of local anesthetic each. Sedation was achieved with midazolam given intravenously when necessary. In group C (n=15) GA was induced with thiopental and maintained with enflurane and N_2O in O_2 by face mask. Blood samples for the determination of lidocaine concentrations (EMIT-test) were taken before the ICNB as well as 10, 20, 30, 60 and 90 minutes after the last injection of the local anesthetic. In order to determine blood concentrations of epinephrine (radio-enzymatic assay) further samples were taken before, 3 and 15 minutes after the beginning of surgery, as well as 30 and 60 minutes following the end of the procedure. ECG and blood pressure were monitored as usual. Side effects and onset of postoperative pain were noted. Finally the patients were asked their opinions concerning the acceptance of the respective anesthetic techniques. Statistical comparisons for epinephrine and lidocaine blood levels were made by Wilcoxon's test. Chi-square test was used to compare the side effects and the patient's demand for postoperative analgesics.

Results. All patients had adequate surgical anesthesia. Duration of surgical procedure did not differ between the groups (mean 33 ± 2 min). Figure 1 presents lidocaine blood levels of group A and B. The average peak level was reached ten minutes after the ICNB in group B and 10 min later in group A. The mean lidocaine blood levels after 10, 30 and 60 min were significantly lower in group A than in group B ($p<0.01$) whereas after 90 min the values did not differ significantly. Signs of systemic toxicity could not be observed in any patient. Due to the technical procedure there was a small pneumothorax in one patient. Figure 2 presents epinephrine blood levels in the three groups. Before and during surgery epinephrine blood levels were higher in group A compared with groups B and C ($p<0.02$). During postsurgical recovery blood levels of epinephrine were higher in groups A and C than in group B ($p<0.02$). Patients receiving GA had far more nausea and vomiting after the anesthesia compared with ICNB, i.e. no patient in groups A and B in contrast to 11 patients in group C ($p<0.01$). Women with ICNB required significantly less analgesics postoperatively than those who had a GA, i.e. six and four in groups A and B respectively 11 in group C ($p<0.01$).

Fig.1

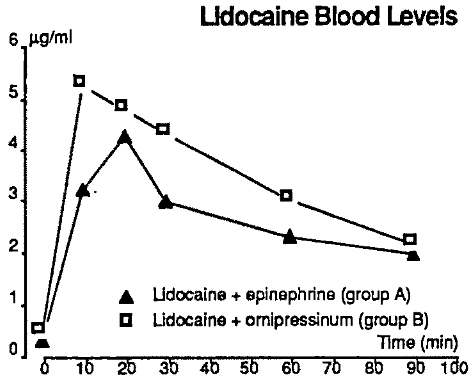
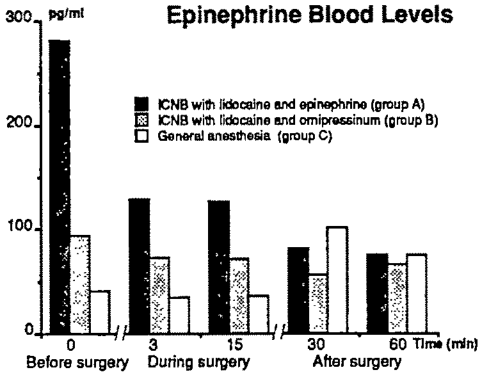


Fig.2



Conclusions. ICNB was shown in our study to be a safe anesthetic technique as efficient as GA for minor breast surgery, providing the additional benefit of prolonged postoperative analgesia. Though lidocaine blood levels were higher in group B than in group A ornipressinum should be preferred as a vasoconstrictor to the local anesthetic solution to avoid higher epinephrine blood levels particularly in patients with severe cardiac disease.

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Title: THE TOXIC EFFECTS OF BUPIVACAINE ARE AGE DEPENDENT IN YOUNG PIGS

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Introduction: It has been suggested that newborns and infants may be at greater risk of toxicity from local anesthetics than are older children because newborns and infants have low plasma concentrations of α_1 acid glycoprotein (AAGP) (1). Six week old dogs anesthetized with halothane and N_2O are more sensitive to the cardiovascular (CV) toxic effects of bupivacaine than are younger or older dogs (2). It has not been determined whether sensitivity to the central nervous system (CNS) toxicity of bupivacaine is age dependent in young subjects. In the present study, we compared the CV and CNS toxic effects of bupivacaine in three different age groups of young pigs.

Methods: After approval from the Animal Care Committee, we studied 18 farm bred pigs age 2 days (2D group, n=6), 2 weeks (2W group, n=6), and 2 months (2M group, n=6). Anesthesia was induced using 70% N_2O/30% O_2 and halothane. The trachea was intubated with a cuffed tube and ventilation was controlled with a Siemens-Elema 900D ventilator. Arterial PCO_2 was maintained at 32-36 mmHg. Anesthesia was maintained with 1.0-1.5% halothane and 70% N_2O during surgical preparation. The ECG and EEG were continuously recorded using a strip chart. Catheters were inserted into 1) the femoral artery for continuous BP measurement, 2) the inferior vena cava (via the femoral vein) for drug administration and, 3) the femoral vein for blood sampling. After muscle relaxation with pancuronium, the pigs were allowed to stabilize for 30 minutes on 70% N_2O/30% O_2 without halothane and were given D_5RL (25 ml/kg) intravenously. Bupivacaine (0.5%) was then continuously administered (1 mg/kg/min) using an infusion pump. The doses were recorded for each of four events: 1) first ventricular dysrhythmia (DYS), 2) first seizure (SZ), 3) isoelectric EEG (ISO EEG) and, 4) asystole (ASYS). Every 5 minutes during the infusion, non-invasive cardiac output was determined (3) and blood was sampled for measurement of plasma concentrations of bupivacaine by HPLC. Plasma was separated and frozen at -80°C for analysis at a later date. Differences among the three groups for doses required to produce each of the four events were compared using one-way ANOVA and the Student-Newman-Keuls test.

Results: The doses of bupivacaine that produced dysrhythmias and seizures were higher in the 2D group than in the 2W and 2M groups (Figure). Dysrhythmias occurred before seizures in each pig. The doses that produced isoelectric EEG and asystole did not differ significantly. Cardiac output was maintained in each pig until immediately before asystole despite seizures and dysrhythmias. Differences among plasma bupivacaine concentrations at each event will be reported.

Discussion: The relative resistance of younger pigs to the effects of bupivacaine suggests that binding with AAGP may be less important in influencing the toxicity of local anesthetics than previously thought. More important influences may be the immaturity of the nervous system in younger animals (4) and the increased volume of distribution for bupivacaine in younger animals (5). Although the cause is unclear, our data suggest that the CV and CNS toxicities of bupivacaine are age dependent, younger animals tolerating higher doses.

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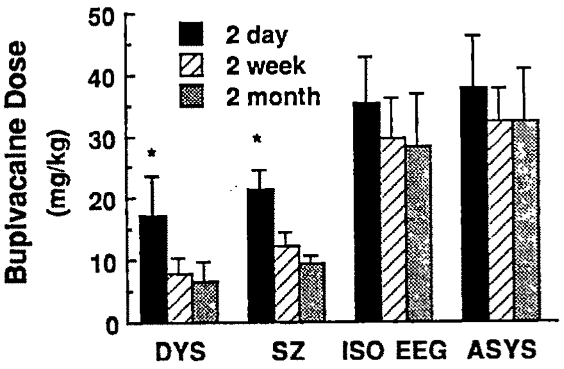

Figure. Bupivacaine doses required to produce CV or CNS toxicity (mean ± SD). * = $p \leq 0.005$ compared to 2W and 2M.

Title: EFFECTS OF HYPOTHERMIA ON NONINVASIVE GAS MONITORING

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Introduction. Transcutaneous oxygen tension (PtcO2) and carbon dioxide tension (PtcCO2) will reflect intraarterial values if skin blood flow is normal, but they will not do so when cardiac index is low (1). End-tidal carbon dioxide (PetCO2) correlates well with temperature-corrected PaCO2 except in cases of large alveolar dead space (2). This study is aimed at defining the relationships between these noninvasive variables and their intraarterial counterparts during hypothermia to 26°C.

Methods. This study was approved by the Committee on Animal Research. Four 50 kg swine were anesthetized with sodium pentobarbital, intubated, and mechanically ventilated. Pancuronium was used to prevent shivering. Each animal was monitored with arterial and pulmonary artery catheters, three PtcO2 and one PtcCO2 probes (each heated to 44°C), and a sidestream PetCO2 monitor (Novametrix 1250). Arterial and mixed venous blood gas tensions were measured by standard 37°C electrodes. Pulmonary artery blood temperature T was decreased slowly by external cooling from 37°C to less than 26°C. At each stable T value, FIO2 and ventilation were both varied to obtain a range of PaO2 and PaCO2 values. Each data set consisted of hemodynamic values, arterial blood gases, and data from all noninvasive monitors. Data were analyzed by correlation and linear regression; statistical significance of changes was examined by Student's two-tailed T test.

Results. The ratio of PtcO2 to PaO2 is called the "transcutaneous index" (O2R). The mean and standard deviation (SD) of O2R in this study were 0.45 ± 0.23 (n = 69). For data having $T < 29$°C, the mean and SD of O2R were 0.43 ± 0.23 (n = 23), which is not significantly different. If we separate the data by FIO2 values (Table 1), we find a significant correlation between O2R and T only for FIO2 = 0.5 (R = 0.83). On the other hand, O2R was found to be strongly related to PaCO2: for PaCO2 = 30 - 44 mmHg O2R is 0.46 ± 0.21, whereas for PaCO2 less than 30 mmHg it is 0.17 ± 0.13 ($P < 0.005$). PaCO2 values above 44 mmHg have little effect on O2R.

PtcCO2 is best correlated with uncorrected (37°C) PaCO2. Defining CO2R as PtcCO2/PaCO2, we find the mean ± SD of CO2R is: T > 33°, CO2R = 1.02 ± 0.083; 29° < T<33°, CO2R = 1.05 ± 0.137; T < 29°, CO2R = 1.02 ± 0.024. CO2R is near unity and is not affected by temperature.

The means and standard deviations of the differences between PetCO2 and PaCO2 in three temperature ranges are given in Table 2. PetCO2 correlates best with temperature-corrected PaCO2 (PaCO2T). The difference between PetCO2 and uncorrected PaCO2 (PaCO2U) increases with falling T to 17.0 ± 5.5 in the lowest temperature range (Table 2).

Discussion. The transcutaneous index O2R has a mean value of 0.8 in adults with a normal cardiac index (1). O2R is lower in pigs than in adult humans, and there is little if any dependence upon core temperature. Surprisingly, O2R is strongly affected by hypocarbia (PaCO2 < 30 mmHg), being reduced to less than half of its normocarbic value. PtcCO2 correlates well with uncorrected PaCO2 values, and the agreement is independent of T. PetCO2 correlates best with temperature-corrected PaCO2, and the difference between the two decreases slightly at lower temperatures.

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Table 1. Transcutaneous index O2R versus temperature at four FIO2 values: correlation coefficient (R), linear regression slope and intercept, std. error of the estimate (SEE).

FIO2	mean	std.dev.	R	slope	intercept	SEE
1.0	0.33	0.16	0.62	0.027	-0.53	0.148
0.5	0.28	0.13	0.83	0.022	-0.43	0.080
0.3	0.44	0.13	0.14	0.004	0.30	0.148
0.2	0.52	0.18	0.21	0.009	0.26	0.207

Table 2. End-tidal - arterial PCO2 difference versus temperature T (mean ± std. dev.), temperature corrected (PaCO2T) and uncorrected (PaCO2U) blood gas values.

T (°C)	PaCO2T - PetCO2	PaCO2U - PetCO2
> 33	8.0 ± 4.2	7.0 ± 4.7
29 - 33	5.5 ± 2.0	15.1 ± 3.5
< 29	4.6 ± 2.9	17.0 ± 5.5

Title: FIBEROPTIC INTRAARTERIAL pHa, PaO2, AND PaCO2 IN THE OPERATING ROOM

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Introduction. Fiberoptic intraarterial measurements of PaO2 using fluorescence-quenching "optode" probes have been reported in both animals and humans (1-3). A combined fiberoptic probe which simultaneously measures pHa, PaCO2, and PaO2 has been used in the intensive care unit (3). Although the three-component optode performs well in-vitro, there have been problems with accuracy in intraarterial applications. This is the first reported study of three-component optode probes inserted into radial artery cannulas of patients undergoing surgical procedures in the operating room.

Methods. Ten patients undergoing surgical procedures under general anesthesia took part in this study, which was approved by the human subjects review committee. All patients required radial artery cannulation for surgical or anesthetic reasons. An 18 gauge 4.4 cm cannula was inserted into the distal radial artery of each patient using the Seldinger technique. The Cardiovascular Devices, Inc. probe was calibrated as recommended by the manufacturer prior to insertion into the arterial cannula. No calibration changes were made after the probe was inserted into the cannula. The probe diameter was nominally 0.63 mm and its tip was near the end of the arterial cannula. The fiberoptic probe contains a thermistor, and the readout provides both patient-temperature and 37°C blood gas values. Blood samples were aspirated through the same arterial cannula for analysis by an IL-813 Blood Gas Analyzer. This instrument was calibrated daily against reference standards. A blood gas specimen was obtained every 20-30 minutes during periods of steady optode readings. Sixty-eight samples were obtained in ten patients. The data were analyzed by linear regression, correlation, bias (mean error) and precision (standard deviation of error).

Results. The presence of the optode probe in the arterial cannula did not interfere with continuous pressure measurements or aspiration of blood samples. No patient experienced thrombotic complications from the use of the 18 gauge cannula. A scattergram plot of the optode PO2 (PoO2) versus 37°C PaO2 values from the blood gas analyzer is shown in Figure 1. Lines of identity and linear regression are shown. Statistics relating optode pH, PO2, and PCO2 to the corresponding values from the blood gas analyzer are shown in Table 1. These include correlation coefficient, linear regression slope and intercept, bias, and precision. A plot of optode error versus time elapsed from probe insertion shows no significant dependence of error upon time.

Discussion. The accuracy and reliability of the optode shown here (Figure 1, Table 1) is improved relative to previous work (2,3). No data have been edited from these results; there were no probes that "failed" to track PaO2. Failures in previous studies were attributed to clot formation or probe impingement on the arterial wall. One earlier study (2) employed an optode recessed 2 mm behind the tip of the arterial cannula, and blood had to be aspirated from the cannula before each optode reading. In the present configuration, optode data were obtained continuously, and showed a rapid response to clinical changes. During one intracranial procedure, a significant air embolism was detected by a rapid fall in PoO2 before the anesthetist noted any abnormalities in his routine monitors. By its intrinsic nature, the PO2 optode should be more accurate at lower oxygen tensions. This is evident in Figure 1. The PO2 accuracy shown here and in Table 1 (R = 0.982, bias = 3.3, precision = 23.8) is near the desired range. The PCO2 accuracy is also clinically acceptable. The PCO2 correlation coefficient is misleadingly low due to the narrow range of PaCO2 values obtained in the study. Further improvement in accuracy is needed in the pH electrode, although it consistently followed trends (Table 1). These data differ from previous results in that an 18 gauge (rather than 20 gauge) arterial cannula was used. This is the first reported intraoperative study of a three-component optode system to yield reasonable accuracy with excellent stability and reliability.

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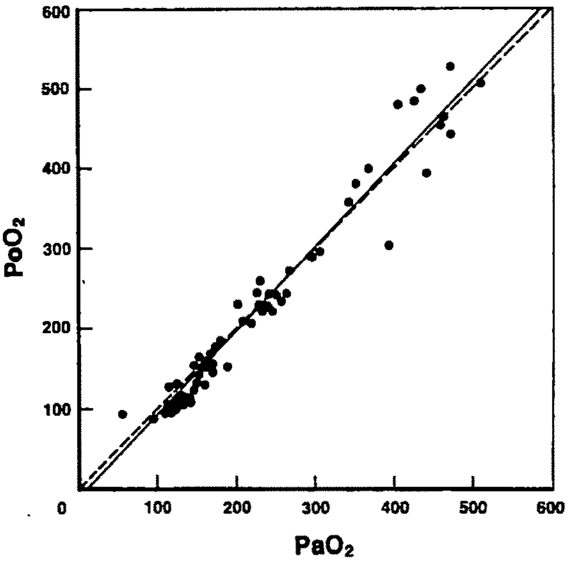
Table 1. CDI Optode pH, PO2, PCO2 versus arterial blood gas values from IL-813.

	pH	PO2	PCO2
Correlation R	.737	.982	.830
Slope	.896	1.05	.956
Intercept	.739	-13.8	-2.38
Bias	-.039	-2.97	-3.82
Precision	.057	23.8	4.54

Figure 1. Optode PO2 (PoO2) versus 37°C PaO2 from IL-813: 10 patients, 68 samples.



TITLE: RESPIRATORY DEPRESSION AFTER ALFENTANIL INFUSION: A COMPARISON OF MIDAZOLAM AND DIAZEPAM PREMEDICATION

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Introduction.

Respiratory depression after narcotic anesthesia is a recognized problem[1]. The time course of this depression is an important factor governing postoperative risks and recovery room stay. While this should be less important after a shorter lived narcotic such as alfentanil (half-life of 90 min), there is a potential for prolonged recovery when the duration of administration is extended. We, therefore, undertook to study the extent and time course of respiratory depression following alfentanil N_2O/O_2 anesthesia in procedures longer than 90 minutes. Because of recent warnings concerning respiratory depression associated with parenteral midazolam, two groups were studied: one received i.v. midazolam and one p.o. diazepam premedication.

Methods.

Eleven patients (ASA class I-III) scheduled for elective lumbar discectomy gave written informed consent to participate in this IRB approved protocol. Patients were excluded if they had a history of active pulmonary disease, obesity (above 110 kg) or current athletic training. Patients were tested with the CO_2 response apparatus and cognitive tests (Trieger dot and digit substitution) prior to surgery. Premedication consisted of either midazolam (2-4 mg i.v.) after initial testing (7 patients) or diazapam (5-10 mg p.o.) 30-45 minutes prior to testing (5 patients). Anesthesia proceeded with pancuronium 0.015 mg/kg i.v. and pre-oxygenation followed by alfentanil 75 µg/kg given over 90 s. Thiopental 1-4 mg/kg was given to complete anesthetic induction. Succinylcholine 1.5 mg/kg provided relaxation for endotracheal intubation. Anesthetic maintenance consisted of N_2O 60-70% in O_2 and an alfentanil infusion begun at 1.5 µg/kg/min and adjusted as clinically indicated. Pancuronium was given according to clinical need and reversed with neostigmine 2.5 mg/atropine 1 mg. Alfentanil was stopped 20-30 min. before the end of surgery. Postoperative times were measured from the discontinuation of N_2O. Postoperative measurements were begun as soon as the patient was alert and cooperative and continued at half hour intervals until further pain medication was requested. Cognitive function was assessed with the Trieger dot and digit substitution tests. Ventilatory status was assessed by the Reed rebreathing method for CO_2 responsiveness. The curve of minute ventilation vs. end tidal pCO_2 was fit by linear regression over its linear part to give the response slope. Simultaneous blood gases were used to confirm accurate end tidal values at the beginning of the test. Any incidence of apnea or arterial desaturation from pulse oximetry were noted. Significant differences in CO_2 response slopes and cognitive tests were determined by repeated measures ANOVA. Values are mean ± S.D.

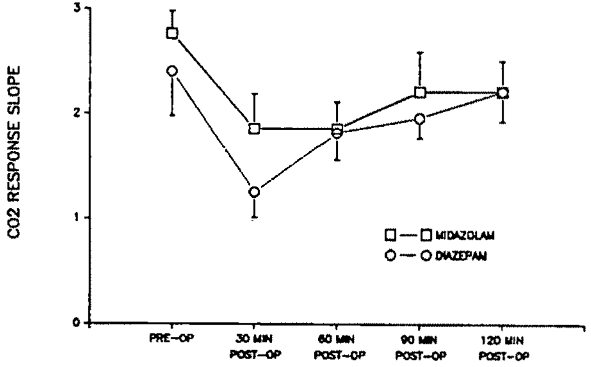
Results.

There were no differences in the age, sex distribution or weight between the groups. Time of surgery and alfentanil dose were also similar averaging 20.5 mg and 185±25 minutes. The midazolam and diazepam groups did not differ significantly even preoperatively (fig. 1). One patient in each group had periods of apnea and arterial desaturation despite supplemental oxygen. This corrected with repeated stimulation. The CO_2 slopes were significantly depressed from control values for all measured postoperative periods. ANOVA, for polynomial contrast, however, showed a significant increasing linear trend for CO_2 responsiveness in the postop period ($p<0.005$). Cognitive tests showed a similar time course.

Discussion.

Post-operative respiratory depression is a problem that can occur after any narcotic supplemented anesthetic. The short acting agent alfentanil is no exception. Its advantageous pharmacokinetics may make this problem of a briefer duration than longer lived agents. The depressed CO_2 responsiveness, clinically observed apneic spell and associated arterial desaturation point to a depressed response that must be monitored and treated. The standard responses of stimulation and encouragement to breathe were all that were necessary to correct this problem. Observation alone did not detect these events before some desaturation had occurred. We therefore recommend that patients receiving narcotic supplemented anesthetics be given supplemental oxygen and monitored with pulse oximetry until they demonstrate an hour of adequate ventilation without stimulation. The choice of benzodiazepine for pre-medication made no difference in this study.

Figure 1. CO_2 response slope (l/min/mmHg ± SE) for midazolam and diazepam groups



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Title: NEUROMUSCULAR EFFECTS AND PHARMACOKINETICS OF MIVACURIUM IN ELDERLY PATIENTS UNDER ISOFLURANE ANESTHESIA.

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Introduction

The pharmacokinetics of the new short-acting relaxant, mivacurium chloride, have recently been studied.[1] This agent is rapidly metabolized by plasma cholinesterase[2], and presumably this accounts for mivacurium's short duration of action. Secondary to this non-organ based elimination, it might be expected that the pharmacokinetics of mivacurium would be only minimally altered in the elderly patient population.

Methods

After giving institutionally approved informed consent, 9 healthy elderly patients (ASA Class I-II, 65-80 y/o) and 8 healthy young patients (ASA I-II, 18-50 y/o) scheduled for elective surgery were studied. Patients were premedicated with diazepam (5-15 mg PO) and morphine sulfate (5-10 mg IM). Anesthesia was induced with thiopental (4 mg/kg) and fentanyl (2-4 ug/kg) IV. The trachea was intubated under isoflurane without the use of relaxants. After intubation, end-tidal isoflurane concentration was adjusted to and maintained at 0.8% in 60% N_2O and O_2. Blood pressure, EKG, O_2-saturation, end-tidal CO_2 and temperature were monitored and recorded. All patients were normoventilated and temperature maintained between 35-37 C. The evoked mechanical response of the ulnar nerve-adductor pollicis system was monitored using supramaximal square wave impulses at 0.15 Hz via steel needle electrodes at the wrist. Following stabilization of the twitch response and 15 minutes of stable end-tidal isoflurane at 0.8%, a single rapid IV injection of mivacurium (0.1 mg/kg) was given over 15 seconds. Blood samples for determination of plasma concentration of doxacurium were drawn from a separate large bore venous sampling catheter at 0,1,2,3,4,7,10,15,20,30,45,60,75, and 90 minutes. Samples were analyzed by high pressure liquid chromatography. The data were analyzed by t-test with a p-value of 0.05 considered significant.

Results

The neuromuscular effects of mivacurium are shown in Table 1. There are no statistically significant differences in any parameters. The pharmacokinetic data fit a three-compartment model in all patients and the data are shown in Figure 2. Again, no statistically significant differences were found.

Discussion

It appears that the normal physiologic changes in organ function seen in elderly patients do not appreciably alter the neuromuscular effects or pharmacokinetics of mivacurium. It is suggested that the rapid metabolism to inactive metabolites by plasma cholinesterase (metabolized at 88% of the rate of succinylcholine hydrolysis[2]) is the primary reason for this observation. This study suggests that mivacurium can be used in the elderly without the need for altering dosage strategies based on pharmacokinetic parameters. Further studies in patients with abnormal plasma cholinesterase, renal dysfunction, and hepatic dysfunction would also seem warranted.

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Table 1

Neuromuscular Effects of Mivacurium (±SE)

	Young (n=8)	Elderly (n=9)
Max Block	99.5±0.5	99.1±.05
Time to Max Block (min)	3.3±0.4	5.0±0.5
Time to 5% Recovery (min)	14.3±1.5	13.4±1.2
Time to 25% Recovery (min)	18.0±1.7	19.9±1.2
Time to 95% Recovery (min)	31.7±3.1	36.9±5.1

Table 2

Pharmacokinetics of Mivacurium (±SD)

	Young (n=8)	Elderly (n=9)
t 1/2α (min)	0.36±0.16	0.43±0.20
t 1/2β (min)	1.97±0.81	1.91±0.53
t 1/2γ (min)	35.4±28.3	31.4±17.4
V_c (ml/kg)	22±19	21±17
V_{dss} (ml/kg)	295±243	292±312
Cl (ml/kg/min)	18.7±8.0	16.9±4.0

Title: ISOFLURANE VS METHOHEXITAL DURING INCOMPLETE CEREBRAL ISCHEMIA IN THE RAT

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Introduction. Both barbiturates and isoflurane have been cited as anesthetic drugs that provide cerebral protection in the face of incomplete global or hemispheric ischemia (1). The proposed mechanism of this protection is by depressing cerebral metabolism. Although both barbiturates and isoflurane can decrease cerebral oxygen consumption ($CMRO_2$) up to 50% there is a question whether either anesthetic provides better brain protection. Recently, Nehls reported that barbiturate-treated monkeys with middle cerebral artery occlusion had better neurologic outcome than isoflurane-treated animals. However, using a similar animal model, Milde et al (2) showed no difference in neurologic outcome between barbiturate and isoflurane treated animals. In order to investigate this question we studied the cerebral protectant activity of methohexital and isoflurane using a rat model of incomplete hemispheric ischemia. We compared neurologic outcome at two levels of ischemia using two doses of each drug.

Methods. This research was approved by the Institutional Animal Care Committee. Male Sprague-Dawley rats weighing 350-450 g were anesthetized, intubated and ventilated with isoflurane in 30% oxygen. Arterial and venous catheters were inserted for blood pressure recording, blood withdrawal and drug infusion. The right carotid artery was isolated and a loose ligature placed around it for later clamping. Screw electrodes were placed on the skull for EEG recording. Rectal temperature was maintained at 37°C and vecuronium was administered as needed to maintain paralysis. In the isoflurane treated animals the anesthetic concentration was adjusted to 1 or 2 MAC. In the methohexital treated animals, isoflurane was discontinued and each animal received a methohexital infusion (low dose = 0.01, high dose = 0.1 mg/kg/min). Following a 30 minute equilibration period the right carotid artery was clamped and either moderate ischemia was produced by maintaining $FiO_2 = 30\%$ with mean blood pressure of 30 mmHg or severe ischemia was produced by decreasing FiO_2 to 20% and mean blood pressure to 25 mmHg. Control rats were maintained on 70% N_2O/30% O_2 during the moderate ischemia challenge and 80% N_2O/20% O_2 during severe ischemia. At the end of the ischemic period the carotid artery was unclamped and the blood slowly reinfused. Each animal received only one dose of test drug and level of ischemia. Arterial PCO_2 was adjusted to 35-45 mmHg by altering ventilation and normal pH was maintained during hypotensive and reinfusion periods with a bicarbonate infusion as necessary. At the end of the recovery the catheters were removed and incisions closed. Neurological deficits were initially evaluated 3 hours after recovery and repeated every 8 hours for 3 days. Scores were rated from 0 to 5 as follows: 0 = normal, 1=paw adduction or abnormal posturing, 2= circling or rolling behavior marked by motor rigidity or weakness, 3 = stimulated seizure activity, 4 = unstimulated seizure activity, 5 = death associated with stroke. Separate groups of similarly treated animals were used to study cerebral blood flow (CBF) and $CMRO_2$ (n=4-5 per group). Regional CBF was measured using radioactive microspheres and $CMRO_2$ by multiplying cortical CBF times arterial-sagittal sinus O_2 content. CBF and $CMRO_2$ were measured in group 1 during N_2O control conditions (test 1), low dose (test 2) and high dose methohexital (test 3). In group 2, CBF and $CMRO_2$ were measured during N_2O (test 1), 1 MAC isoflurane (test 2) and 2 MAC isoflurane (test 3).

Results. All animals lived for at least 3 hours after recovery from hypotension. Rats that died showed progressive signs of severe stroke including abnormal paw positioning during handling, circling and rolling behavior followed by stimulation-induced and non-stimulated seizures. Differences in neurologic outcome among treatment groups are shown in table 1. Treatment with methohexital and isoflurane resulted in decreased neurologic deficit scores compared to N_2O Two MAC isoflurane also produced significantly improved outcome compared to N_2O following severe ischemia. $CMRO_2$ showed a comparable dose related depression during methohexital and isoflurane anesthesia to levels 45-50% of control values which was coincident with burst suppression or flat line EEG.

Discussion. The rat model used in this study produces cerebral ischemia by unilateral carotid ligation combined with hemorrhagic hypotension. Previously we have found that neurologic outcome correlates with the degree of ischemia and neurohistopathology. Our results show that outcomes were similar for both isoflurane and methohexital treated rats exposed to moderate ischemia. Deficit scores increased with severe ischemia in all groups but 2 MAC isoflurane produced significantly better protection than N_2O. Isoflurane's ability to provide better protection during severe ischemia is consistent with the theory that greater $CMRO_2$ depression produces more protection.

Table 1. Deficit Scores Following Incomplete Cerebral Ischemia

	Moderate Ischemia	Severe Ischemia
N_2O	4.6	5.0
low dose methohex	1.3*	4.6
high dose methohex	1.8*	4.6
1 MAC isoflurane	1.8*	3.9
2 MAC isoflurane	1.4*	2.8*

* = $P<0.05$ compared to N_2O

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Title: THE NEW "PIG-TAIL" TIPPED CENTRAL VENOUS CATHETER--A DESIGN TO ELIMINATE VASCULAR PERFORATION

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Introduction. Late perforation of vascular structures by a central venous catheter tip is an unusual but potentially lethal complication. Perforations are most commonly caused by the continuous impingement of the catheter tip against the walls of vascular structures which are in motion[1]. Catheter stiffness, angle of impingement, and irritative catheter material all play a role in catheter-induced vascular perforation. We postulate that the risk of catheter perforation could be reduced by preventing continuous impingement of the tip against the vessel wall. This is possible by using a specially designed "pig-tailed" tipped catheter (Cook, Inc. Bloomington, In; see Fig.) In vitro evidence[2] has suggested that this curved tip catheter is significantly superior when compared to other straight-tipped catheters and has been demonstrated to have a markedly low perforating potential. This report describes our initial successful experience with the new CVP catheter in humans.

Methods. The "pig-tail" tipped central venous catheter used in this study is a triple lumen soft polyurethane catheter 20 cms in length. Approval of the Human Investigation Committee was obtained for use of the catheter in patients who required a central line as part of their surgical therapy. The catheter was placed, using the Seldinger technique[2] (J-wire), in a jugular or subclavian vein and advanced to a depth of 15-18 cms, the catheter was then sutured in place and covered with an antibiotic dressing. A chest x-ray (CXR) was obtained in all patients to determine catheter tip position. Any difficulties encountered during placement were noted as was the incidence of arrhythmias. All patients were followed by a research nurse until the catheter was removed. Patients frequently had additional CXRs after placement because of unrelated medical conditions; this allowed us to determine whether the catheter position changed significantly after placement. The incidence of infection, duration of catheter use, and all catheter-related complications were recorded.

Results. We placed the new "pig-tail" tipped CVP catheter (Figure) in 120 patients whose ages ranged from 18 to 99 years. 60 patients were males. The majority of catheters were placed via the right internal jugular (IJ) vein (Table) and their tips were usually sited low in the superior vena cava (SVC). Catheter insertion over the guide wire was accomplished easily. Transient inconsequential arrhythmias were noted in 15 patients, usually in response to manipulation of the guide wire. There were 2 complications related to catheter placement: 1 localized cervical hematoma and 1 pneumopericardium. The latter may have been related to subdiaphragmatic retraction during gastrointestinal bypass surgery in a morbidly obese patient rather than to IJ puncture. The pneumopericardium resolved spontaneously. The catheters remained in place for a mean of 5.6 ± 3 days. No difficulty was encountered in recording the central venous pressure tracing with any of the catheters. Migration of catheter tip occurred in 4 patients but was so minimal that it may represent only altered radiologic technique or difference in CXR interpretation. There were no perforations of vascular structures. Catheter sepsis occurred in 5% of patients, which is consistent with previously reported sepsis rates. None of the patients had clinical evidence of thrombosis of the vessels in which the catheter was placed. There was no difficulty in removing the catheter from any patient.

Discussion. The new "pig-tail" CVP catheter appears promising and may represent a substantial improvement over conventional straight-tipped catheters. This initial experience demonstrates that the catheter is relatively easy to insert and is not associated with any new or unexpected problems.

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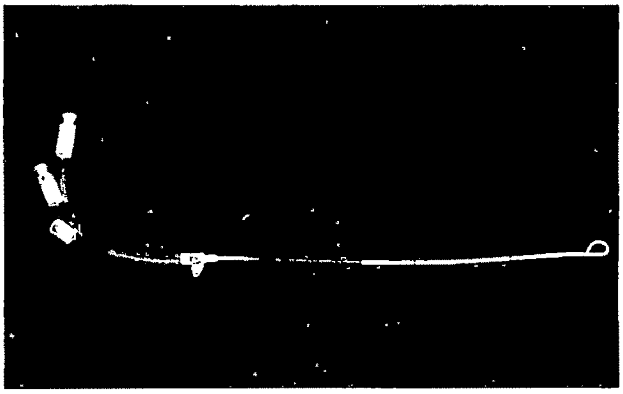
TABLE

			Catheter	Tip	Termination
Entry Site	No.	Duration*	SVC	RA	Other†
R Int Jug Vein	101	5.5	73	24	4
R Ext Jug Vein	4	7.7	1	3	-
R Subclav Vein	3	7.7	2	1	-
L Int Jug Vein	5	6.3	3	1	-
L Ext Jug Vein	3	6.3	2	-	1
L Subclav Vein	4	3.8	4	-	-
Total:	120	5.6	86	2	5

* mean in days
† 3 in R innominate vein
2 in R ventricle

FIGURE
The New "Pig-tail" Tipped Central Venous Catheter



Title: COMPARISON OF THE MECHANICAL AND ELECTROMYOGRAPHIC RESPONSES FOLLOWING ATRACURIUM ADMINISTRATION DURING FENTANYL AND ISOFLURANE ANESTHESIA

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Introduction. The basis of neuromuscular monitoring is the stimulation of a peripheral nerve and the measurement of the evoked electrical (EMG) or mechanical (MMG) responses of the muscles which it supplies. Previous studies have shown that MMG twitch height depression exceeded EMG depression during halothane anesthesia (1,2,3). While EMG and MMG responses are virtually equivalent during the early phases of N_2O:fentanyl (F) anesthesia (4) the MMG is more depressed during recovery. There is no information on comparison of EMG and MMG responses during isoflurane (I) anesthesia. The EMG and MMG responses have been examined in the present study following atracurium administration during I and F anesthesia.

Methods. 40 patients, aged 16-65 yr, ASA I or II, presenting for elective surgery were included in the study with their informed consent and Ethical Committee approval. Following diazepam premedication, and induction of anesthesia with thiopental 4-5 mg/kg, patients were randomized to receive I 0.75% (1.5 MAC end-tidal in 70% N_2O) or increments of F 50-100 ug as required. Ventilation was adjusted to maintain normocarbia. The evoked integrated EMG (IEMG) responses were recorded from one hand using the Datex Relaxograph, while from the other the mechanical responses of adductor pollicis were recorded using the Myograph 2000. Both monitors operated in the train-of-four (TOF) mode at 2Hz every 10 s. After determination of the supramaximal stimuli and stabilization of control twitch heights, patients in both groups were randomly allocated to receive atracurium (A) 0.125 mg/kg or 0.45 mg/kg. Each group contained 10 patients. The height of T1 at maximum block was recorded for both MMG and IEMG in patients receiving 0.125 mg/kg of A. In the 0.45 mg/kg groups the times from administration of A to the development of complete neuromuscular block and to recovery of the first twitch (T1) in the TOF to 25% of control twitch height were recorded for both monitors. Results were subjected to analysis of variance and two sample t-tests as appropriate.

Results. Following 0.125 mg/kg of A the degree of block achieved was greater in the I groups with both types of monitoring but the difference was significant only with IEMG monitoring (Table 1). Table 2 shows the onset and duration of neuromuscular block in patients given 0.45 mg/kg of A. MMG monitoring showed shorter onset times under both types of anesthesia but the difference was significant only in the case of I ($p<0.05$). IEMG showed a significantly longer duration to T1 of 25% ($p<0.05$) during F anesthesia. This time was also significantly longer during I anaesthesia in comparison to F using MMG monitoring.

Table 1. T1% at maximum block with A 0.125 mg/kg and F,and I anesthesia.
Mean (±SEM). *$p<0.05$ +$p<0.05$

		F	I
T1% of control	MMG	30.3(±4.5)*	26.0(±8.0)
	IEMG	41.1(±7.5)*+	30.2(±2.7)+

Table 2. Onset and duration of block with A 0.45 mg/kg and F, and I anesthesia.
Mean (±SEM). *$p<0.05$ +$p<0.05$

		F	I
onset (s)	MMG	128.2(±12.3)	103.2(±5.9)*
	IEMG	160.6(±14.5)	132.4(±9.8)*
duration (min)	MMG	32.8(±2.1)*+	44.5(±2.2)*
	IEMG	40.1(±2.6)+	45.9(±2.2)

Discussion. The present study confirms the potentiating effect of I on neuromuscular effects of A although the differences were not always significant. IEMG using a Datex Relaxograph has been advocated as an alternative form of monitoring the neuromuscular block. The present study has shown that it does not give the same results consistantly in comparison to MMG monitoring. The difference in the results of the two methods of monitoring is more marked and significant during narcotic anesthesia and may be due to the potentiating effect of the volatile agent. The exclusive use of IEMG monitoring in place of MMG monitoring does not appear to be justified.

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TITLE: EVALUATION OF TRANSDERMAL FENTANYL FOR MULTI-DAY ANALGESIA IN POSTOPERATIVE PATIENTS
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Introduction: Inadequate analgesia can be a major complaint following most surgical procedures. One concern with parenteral administration of narcotics for postoperative pain relief is the wide fluctuations observed in the plasma concentrations and the associated periods of inadequate analgesia or the risk of respiratory depression. Fentanyl, a potent synthetic opioid, has been incorporated into a transdermal therapeutic system (TTS) which consists of a fentanyl reservoir and a rate-limiting membrane to provide constant release of fentanyl. The purpose of this investigation was to evaluate the safety, efficacy and the pharmacokinetics of fentanyl following multiple TTS patch applications for analgesia in post-surgical patients.

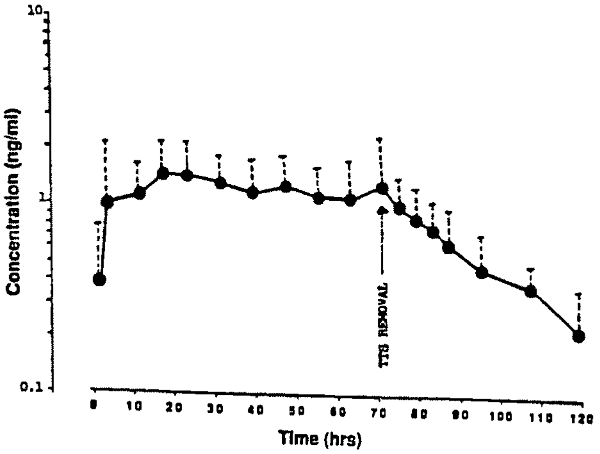
Methods. Nine patients (ASA I-III), ages 56-77 years, scheduled to undergo intraabdominal colorectal surgery, gave their written informed consent to participate in this IRB approved study. No patients with a prior history of chronic narcotic use, liver dysfunction, CNS deficit, PCO_2 greater than 45 torr, body weight less than 50 kg or greater than 100 kg were included in this study. Approximately two hours prior to surgery, the TTS patch delivering 75 µg/hr of fentanyl was placed on the upper chest of the patients. Premedication was with diazepam (10 mg, PO) one hour prior to induction. Anesthesia was induced with thiopental (4 mg/kg) with intubation facilitated by succinylocholine (1.5 mg/kg). 300 µg of fentanyl was also given during induction and the first hour of the case. Maintenance of anesthesia consisted of N_2O/O_2 (60/40 ratio), isoflurane and pancuronium as needed. The TTS patch was left in place for 72 hours. Twenty serial blood samples were obtained for up to 48 hrs following the removal of the last TTS patch (total 120 hrs) for determination of serum, fentanyl concentrations by RIA. If needed, additional postoperative analgesia consisted of morphine sulfate (2 mg, IV) in the recovery room and morphine sulfate (5 mg, IM) every four hrs thereafter. Vital signs, degree of pain (visual analog scale, 0=none, 9=maximum) and sedation were monitored frequently until 12 hrs after the removal of the last TTS patch. Lagrange technique was employed to measure the total area under the plasma concentration - time curve (AUC) and the elimination half-life of fentanyl for each patient. Average plasma concentration (cp) of fentanyl was measured as the ratio of AUC/τ where τ is the duration of fentanyl administration (72 hr). Data is presented as mean (±SD).

Results: Figure 1 and Table 1 summarize the results of the study. Due to sampling problems, the pharmacokinetic analysis were performed for only 8 patients. The mean terminal elimination half-life of fentanyl was 19.6 (5.2) hrs. The mean expected steady-state serum concentration of fentanyl was 1.5 (0.5) ng/ml. Vital signs remained stable and within normal limits during the entire study with minimal patient sedation. Skin reactions to the patch were absent except for transient mild erythema and post patch removal itching in one patient. Visual analog pain scores were quite variable on the first postoperative day ranging from 0 to 9. This variability was less on the 2nd and 3rd postoperative days.

Table One summarizes results

	DAY 1	DAY 2	DAY 3
Range: Mean Visual Analog Pain Score	1.12-1.7	1.12-5.37	0.87-4.87
Range of Mean Resp. Rates	15-20.5	15.2-21.5	17.2-23.7
Nausea	0%	0%	0%
Vomiting	0%	0%	0%
mg supplemental morphine/pt	11.5	11.25	10.6
number patients	10	6	7

*35% morphine used on Day 1 was given in recovery room within the first 3 hours.



Discussion: The TTS (fentanyl) patches were well tolerated in all patients. Pain control was good with 8 of 9 patients saying that they would want the patch in future surgeries. Nausea and vomiting were absent with sedation being minimal. The mean elimination half-life of fentanyl in this study is longer than those following IV administration most likely due to continued absorptions of fentanyl from the skin depot. Although the mean plasma fentanyl concentration seems elevated, clinical respiratory function was good with respiratory rates always falling within acceptable ranges. Several isolated blood gases showed normal pH and pCO_2's, although the mean documentation of the degree of respiratory depression was not done. Overall the system appears to be an important advance in the treatment of perioperative pain.

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Title: COLOSTRUM MORPHINE CONCENTRATIONS FOLLOWING EPIDURAL ADMINISTRATION

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Introduction: Epidural morphine is popular for prolonged analgesia in postpartum patients. Little information is currently available on how much morphine is excreted in the colostrum or breast milk following epidural administration. This study reports morphine and morphine-3-glucuronide (M3G) concentration in the colostrum of patients who received epidural morphine for postoperative pain.

Methods: The protocol was approved by the institutional review board and patients (n=6) gave informed consent. Ringers lactate 1200 ml was used for prehydration. A T4 sensory level was induced with 2% lidocaine with 1 : 200,000 epinephrine (20 ± 4 ml, 1SD). Morphine sulfate (Duramorph) 5 mg was administered via the epidural catheter immediately after delivery. Blood and urine samples were collected at 24, 48, and 72 hours after the epidural morphine injection, and the first colostrum samples were collected as soon as the patients began lactation (24 to 100 hours after morphine administration). Three different extraction techniques were investigated using perchloric acid, hydrochloric acid, or chloroform-ethanol mixture, and the one using HCl yielded the best recovery of both morphine and M3G. One hundred µL of 0.06 M HCl was added to the colostrum samples to precipitate the lipids and proteins. The samples were heated (10 min.), then centrifuged (30 min., 8000 rpm) and the supernatant was harvested for analysis. Free (unconjugated) morphine concentration was measured using a specific radioimmunoassay (RIA) (0.3% cross-reactivity with M3G, Coat-A-Count, Diagnostic Products Corp, Los Angeles, CA). Conjugated morphine concentrations were determined from total morphine concentrations, which were measured following hydrolysis of the conjugates at 37° C for 24 hrs with glusulase (1) (Endo Labs, Garden City N.Y.; 4000 units beta glucuronidase + 700 units sulfatase).

Results: Plasma morphine concentrations for conjugated and free morphine were below the sensitivity of the assay (<0.6 ng/ml). However, urine morphine concentrations at 24, 48 and 72 hours were several thousand times higher than the colostrum morphine concentrations. Conjugated morphine was detected in all colostrum samples, but only in two patients was free morphine detected (Table). The ratio of free to conjugated morphine appears in the Figure.

Discussion: The data show tha epidurally administered morphine does ente breast milk. However, compared to urinar excretion, breast milk concentrations ar low. Although plasma morphine levels wer undetectable, some morphine was detectabl in the colostrum. Most of the morphine i the colostrum is in the conjugated form, an thus pharmalogically inactive. Due to th low oral to parenteral efficacy ratio o morphine, it is unlikely that the neonat will appreciably be affected.

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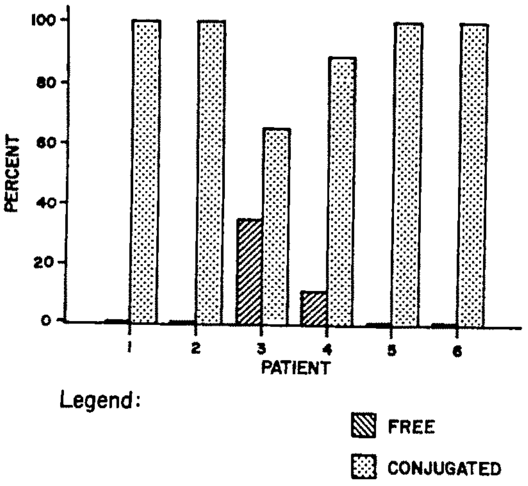
Table

BREAST MILK MORPHINE (NG/ML)

#	TIME	M(F)	M(C)
1	24	0.0	4.2
2	24	0.0	4.2
3	28	4.5	8.6
4	29	0.6	4.9
5	53	0.0	2.1
6	100	0.0	1.2

Legend: Time = hours after administration, M(F) = free morphine, M(C) = conjugated morphine



Title : SINGLE IV BOLUS ESMOLOL PRIOR TO RAPID SEQUENCE INDUCTION EFFECTIVELY BLUNTS THE INTUBATION RESPONSE

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INTRODUCTION. Laryngoscopy and intubation are periods associated with cardiovascular stress that can result in patient mobidity and mortality. Rapid sequence induction (RSI), while diminishing the potential for aspiration, increases cardiovascular stress. Numerous drugs and tech- niques have been employed to blunt hemodynamic responses to intubation. One new approach may be the use of esmolol, a new i.v. selective B_1 blocker with a half-life of 9 min. In this study hemodynamic changes to RSI were evaluated immed- iately following a rapid single bolus injection of esmolol.

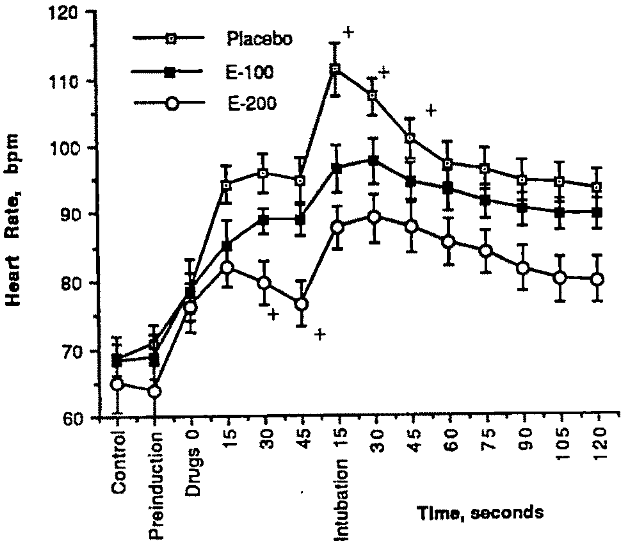
METHODS. After approval by the Institutional Human Research Committee, 32 ASA I and II patients scheduled for elective surgery were studied in a double-blinded fashion. Lorazepam (2 mg) was given PO 90 min prior to induction. ECG, mean arterial blood pressure (MAP), measured by radial artery catheter, and beat-to-beat stroke volume (SV), determined by impedance cardiography, were monitored. Cardiac output (CO), total peripheral resistance (TPR) and rate pressure product (RPP) were calculated. Twenty min after instrumentation, baseline hemodynamic values and a blood sample for norepinephrine (NE) level were obtained; oxygen was administered by mask and vecuronium (0.01 mg/kg) was given. Ten subjects received 100 mg of esmolol (E_{100}), 10 received 200 mg of esmolol (E_{200}), and 12 received placebo (P). Each dose was administered as a 20 ml i.v. bolus over 5 sec followed by a saline flush. This was followed by RSI with cricoid pressure, sodium thiopental (5 mg/kg) and succinylcholine (2 mg/kg). After 1 min patients were intubated, 70% N_2O in O_2 was initiated and monitoring was continued.

RESULTS. Analysis of variance and Dunnett's t-test were applied to compare group responses. Baseline heart rate (HR), MAP, SV, CO, TPR and RPP were similar among groups (table). Esmolol attenuated the pre-intubation tachycardia produced by sodium thiopental (figure). Maximal changes in HR, MAP and RPP occurred 30 sec after intubation; these responses were significantly blunted ($P<0.05$) in the two esmolol groups. Responses of the E_{200} were most attenuated but this did not differ significantly from the E_{100} group. The rise in NE and TPR and the decline in CO was not altered significantly by esmolol.

DISCUSSION. The technique of continuous infusion of esmolol prior to induction has been shown to blunt the cardiovascular responses to intubation.[1] In this study, analysis of beat-to-beat hemodynamic variables showed that HR and MAP changes with RSI were effectively blunted by bolus esmolol while peripheral sympathetic responses (TPR and NE) were not diminished. Since tachycardia may be more strenuous on the heart than an increase in afterload,[2] the B_1-blocking effect of esmolol may protect the heart during RSI. Rapid i.v. injection of esmolol prior to RSI is a simple, convenient and effective technique that should be considered for blunting hemodynamic responses to intubation.

		Control	Peak Intubation+
	P	68 ± 3.0	107 ± 2.8
HR,	E_{100}	68 ± 4.0	98 ± 3.2*
b/min	E_{200}	65 ± 4.0	89 ± 3.6*
	P	5.7 ± 0.4	4.8 ± 0.3
CO,	E_{100}	5.6 ± 0.4	4.2 ± 0.5
l/min	E_{200}	5.8 ± 0.4	3.9 ± 0.4*
	P	96 ± 1.8	140 ± 4.6
MAP,	E_{100}	93 ± 3.7	124 ± 6.2*
mmHg	E_{200}	89 ± 2.4	121 ± 5.2*
	P	1329 ± 103	2537 ± 129
TPR,	E_{100}	1392 ± 142	2623 ± 283
units	E_{200}	1271 ± 112	2758 ± 381
	P	9.5 ± 0.5	19.3 ± 1.2
RPP,	E_{100}	9.3 ± 0.7	15.6 ± 1.7*
$\times 10^{-3}$	E_{200}	8.6 ± 0.5	13.6 ± 0.9*

mean ± SEM, Units = $dyne \cdot sec \cdot cm^{-5}$
* = $p < 0.05$ vs placebo, P = placebo
E_{100} = 100 mg esmolol, E_{200} = 200 mg esmolol
+ = All intubation responses significantly different from control



+ = Significantly different from other two groups, P<0.05

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TITLE: PREVENTION OF POSTOPERATIVE NAUSEA WITH DIMENHYDRINATE (DRAMAMINE) AND DROPERIDOL (INAPSINE)

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INTRODUCTION Nausea is one of the most frequent deleterious side effects of general anesthesia. Droperidol, a butyrophenone, with central cholinergic activity, is commonly used to prevent postoperative nausea. Dimenhydrinate, an antihistamine which blocks the H_1 receptor, has proven to be an effective and inexpensive agent for the prevention of motion sickness, but its efficacy in the prevention of postoperative nausea has never been evaluated. This study compared the efficacy and safety of droperidol (inapsine) and dimenhydrinate (dramamine) in the prevention of postoperative nausea.

METHODS This study was approved by our hospital Institutional Review Committee. Two hundred and fifty adult patients undergoing elective outpatient surgical procedures were randomized into one of three study groups: 1) droperidol (inapsine) 1.25 mg, 2) dimenhydrinate (dramamine) 20 mg, and 3) placebo. The study drugs were administered intravenously, in a double blind manner, prior to the induction of anesthesia. Anesthesia was induced in all cases with methohexital and was maintained with O_2, N_2O and isoflurane. Airway was maintained with either an endotracheal tube or anesthesia mask. No anticholinergic agents were administered. All patients were evaluated postoperatively until the time they were discharged home to determine whether nausea was present. The time necessary for post-anesthesia recovery (PAR) and total time until discharge were recorded. All patient evaluations were performed by a trained recovery room nurse blinded to patient group assignment.

RESULTS Thirty-four percent of patients in the placebo group became nauseated in contrast to twenty-one percent of the patients in the droperidol group and eight percent of the dimenhydrinate group. Tests of significance by analysis of variance demonstrated a significant difference in the frequency of nausea between the placebo group and the two treatment groups. In addition there was a significantly lower incidence of nausea in the dimenhydrinate (dramamine) treated group than the droperidol (inapsine) treated group. There was no difference between groups in the sex or age of the patient or the length of the anesthetic. There was no significant difference in the incidence of nausea between those patients whose airways were managed by endotracheal tube or mask. The time spent in the PAR and the total time from the end of surgery until discharge home were similar in all groups. There were no instances of excessive postoperative somnulence, dizziness, tinnitus, diplopia or nervousness in any treatment group.

DISCUSSION Several studies, including this study, have shown that droperidol (inapsine) is effective in preventing postoperative nausea. This study demonstrates that dimenhydrinate (dramamine) also is effective in preventing postoperative nausea and is superior to droperidol in its antiemetic action. The dopaminergic receptor activity of droperidol is thought to account for its antiemetic actions. The mechanism thought to account for the anti-motion sickness effect of dimenhydrinate is a combination of primary H_1 blocking effect and a central anticholinergic effect. The mechanism of action responsible for the superior antimetic effect of dimenhydrinate compared to droperidol is not clearly understood.

TABLE I

	Nauseated	Not Nauseated	Total
Dimenhydrinate (Dramamine)	6 (8%)+*	69	75
Droperidol (Inapsine)	17 (21%)#	63	80
Placebo	32 (34%)	63	95

Numbers represent absolute numbers of patients. The percent of patients in each group that became nauseated is given in parenthesis.
+ $p < 0.01$ compared to placebo group
# $p < 0.05$ compared to placebo group
* $p < 0.05$ compared to droperidol group

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Title: HYPOTENSION, BRADYCARDIA AND MYOCARDIAL DEPRESSION WITH SUFENTANIL/MIDAZOLAM/VERCURONIUM IN DOGS

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Introduction: Narcotic-based anesthesia is associated with a relative lack of untoward hemodynamic sequelae. Amnesia from narcotics alone is not guaranteed; therefore, other agents such as benzodiazepines have been utilized as amnestic adjuncts. However, hypotension and decreased systemic vascular resistance (SVR) have been reported in humans with benzodiazepines and sufentanil (1-2). We sought to determine if a sufentanil/midazolam combination in clinically relevant doses was associated with consistent adverse hemodynamic actions when administered to awake, nonpremedicated dogs. We chose the muscle relaxant vecuronium to avoid the cardiovascular effects of other relaxants.

Methods: (Precatheter placement) Following institutional approval, nine mongrel dogs (18-29 kg) were anesthetized with thiopental, intubated and maintained with air/O_2/halothane 1-2.5% and spontaneous ventilation. Using aseptic technique, precatheters were placed in the right external jugular vein and right internal carotid artery. The catheters were filled with heparin solution and tunnelled to subcutaneous pouches. The sites were closed and the animals were extubated and recovered from anesthesia. Studies were performed no sooner than 72 hours following surgery and the animals had no evidence of ill health.

(Experimental protocol) The dogs were familiarized with the laboratory and under local anesthesia (1% lidocaine) the precatheters were exteriorized. A 7.5F thermodilution pulmonary artery catheter was placed and continuous pressure recorded. An 8F Millar microtip pressure transducer catheter was advanced so that the distal transducer was in the left ventricle and the proximal transducer was in the aorta and pressures continuously recorded. Continuous cardiovascular measurements included: arterial blood pressure (BP), pulmonary artery pressure (PAP), central venous pressure (CVP), left ventricular end-diastolic pressure (LVEDP), ECG and calculated heart rate (HR). Dp/dt was obtained using a Hewlett Packard 8814A derivative computer. Thermodilution cardiac output (CO) measurements were obtained in triplicate. Derived hemodynamic parameters included stroke volume (SV) and SVR. Hemodynamic measurements were made prior to drug administration and at 1, 5, 10, 15, 20, 25, and 30 min after 13 ug/kg sufentanil, 0.15 mg/kg midazolam and 0.15 mg/kg vecuronium IV. The dogs were intubated at 40 ± 6 seconds and mechanically ventilated. All values are expressed as mean ± SEM. Statistical analysis was performed using a two-way analysis of variance, with significance of $p<0.05$.

Results: The sufentanil/midazolam combination produced a significant decrease in HR (50%), CO (36%), dp/dt (13%), and BP (18%). However, LVEDP, SV, CVP, and SVR increased. The decrease in BP was transient but the other hemodynamic changes were sustained for the 30 minute observation period. Severe bradyarrhythmias were observed in 6/9 animals, including brief periods of asystole in 3/9.

Discussion: The depression of CO appears to be directly related to the significant fall in HR. However, the increases in LVEDP, CVP and depression of dp/dt indicates decreased myocardial function. The increase in SVR and recovery of BP may have been due to a compensatory sympathetic response. These consistent hemodynamic effects seen in a dog model, confirm earlier reports of cardiovascular instability in humans. We believe that caution should be exercised when using this drug combination especially in those with pre-existing cardiovascular compromise.

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(This study was supported in part by USUHS grants CO8028 and RO7682.)

TABLE 1

CARDIOVASCULAR MEASUREMENTS IN SUFENTANIL/MIDAZOLAM/VECURONIUM ANESTHETIZED DOGS (n=8)
TIME (min)

	0	1	5	30
HR (beats/min)	118±10	59±4^{c}	61±4^{c}	64±7^{c}
CO (l/min)	3.4±0.3	2.3±0.3^{a}	2.2±0.2^{a}	2.6±0.4
dp/dt (torr/sec)	3094±275	2687±339^{a}	2593±205^{a}	2531±307
MABP (torr)	95±6	78±6^{a}	90±10	91±11
LVEDP (torr)	11±2.7	17±2.9^{c}	21±2.9^{c}	22±4.2^{c}
CVP (torr)	5.9±1.7	7±1.5^{a}	9.3±1.7^{a}	8.6±1.7^{a}
SVR (dynes-sec-cm^{-5})	2168±179	2661±389	3027±426^{a}	2776±537
SV (ml/beat)	30±3	39±3	37±3	40±2^{b}
pH	7.37±0.01	7.37±0.01	7.37±0.02	7.31±0.03^{a}
pAO_2 (torr)	90.3±1.3	83.0±9.3	93.3±4.7	92.7±6.1
$pACO_2$ (torr)	37.1±1.3	37.8±2.3	35.5±2.0	37.5±2.8

$^{a}p<0.05$ $^{b}p<0.01$ $^{c}p<o0.001$

Title: A COMPARISON OF LIDOCAINE ADMINISTRATION ROUTES FOR THE PREVENTION OF HEMODYNAMIC RESPONSES TO INTUBATION

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Introduction. The risks associated with the hemodynamic responses to laryngoscopy and intubation are well recognized. The aim of this study was to compare various administration routes of lidocaine, used to blunt the hemodynamic responses to intubation, during a fentanyl induction for myocardial revascularization (CABG).

Methods. The study population consisted of patients scheduled for elective CABG surgery. After approval by the Human Investigations Committee, all study participants gave written informed consent. Patients were randomly assigned to one of three groups:

Group I - Fentanyl + laryngotracheal (LT) lidocaine (2mg/kg) immediately before placement of the endotracheal tube.

Group II - Fentanyl + intravenous lidocaine (1.5m/kg).

Group III - Fentanyl + topicalization of the oropharynx with 20cc viscous lidocaine 2% + superior laryngeal nerve blocks.

All scheduled anginal and antihypertensive medications were given the morning of surgery. Premedication consisted of morphine sulfate 0.1mg/kg IM and scopolamine 0.005mg/kg IM.

Prior to induction, a radial arterial catheter, peripheral IV, and a flow directed thermodilution pulmonary arterial catheter were placed percutaneously under local anesthesia. Patients in group III performed a "mouthwash and gargle" with 20ml of viscous 2% lidocaine and swallowed any residual lidocaine. A continuous recording of the ECG, mean arterial pressure (MAP), pulmonary arterial (MPAP), and central venous pressure (CVP) was obtained for subsequent analysis. Induction consisted of 3 minutes of preoxygenation followed by fentanyl 25ug/kg and pancuronium 0.15 mg/kg in incremental fashion.

Three minutes prior to intubation, and 2 minutes after the conclusion of the above induction sequence, IV lidocaine 1.5mg/kg bolus or a bilateral superior laryngeal nerve block, with 2cc of lidocaine 2% applied in a standard fashion, were given to groups II + III respectively. Group I received LT lidocaine 2mg/kg immediately prior to the placement of the endotracheal tube.

Measurement of the heart rate, MAP, CVP, PAP, and cardiac output (CO) were performed 1 minute prior to intubation (Baseline), 1 minute after the completion of induction, 1 and 5 minutes after intubation.

Statistical analysis consisted of repeated measures ANOVA with differences considered statistically significant at $P<0.05$.

Results. Twenty-one patients were studied, 6 in group I, 9 in Group II, 6 in Group III. The groups did not differ with regard to sex, weight, age, time for intubation, history of hypertension or history of B-blocker therapy. Baseline hemodynamics were not significantly different between groups. (see figure)

With induction of anesthesia HR increased significantly, MAP decreased, and no significant changes were noted for MPAP, or cardiac output.

No further changes were noted at one or five minutes after intubation in any of these variables. No significant differences were observed between any of the groups.

Discussion. Recently, Mark and Horrow[1] have shown that IV lidocaine 1.5mg/kg attenuates the hemodynamic responses to intubation in patients anesthetized with 15-25 ug/kg of fentanyl. The current study demonstrates in a similar group of patients that the hemodynamic effects of induction and intubation are not significantly different when lidocaine is administered laryngotracheally, intravenously or topically. Since laryngotracheal lidocaine produces minimal systemic or cardiovascular effects, its use is recommended if lidocaine is selected as an adjunct to 25ug/kg fentanyl in patients with coronary artery disease.

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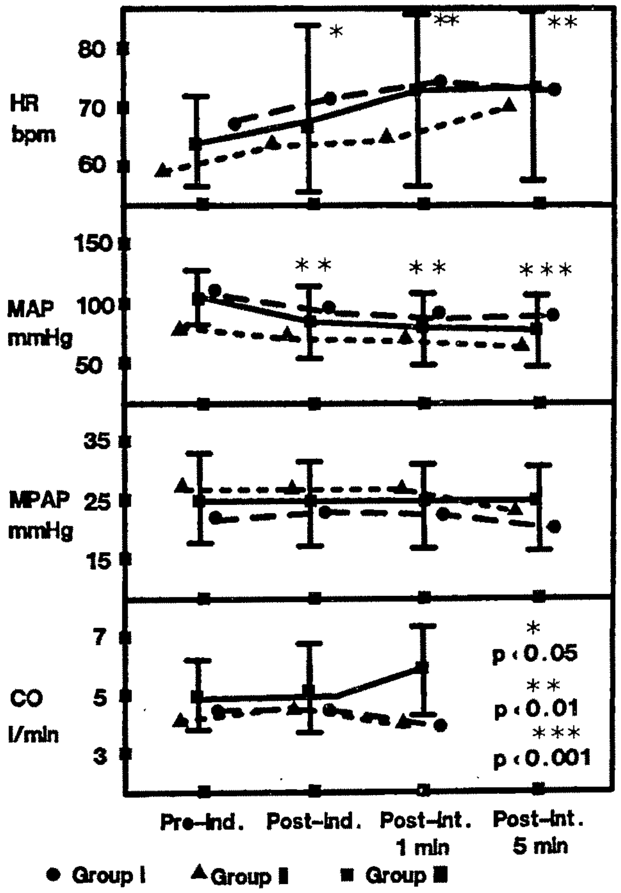

Title: INSPIRED GAS HUMIDIFICATION PREVENTS INTRAOPERATIVE HYPOTHERMIA IN INFANTS AND CHILDREN

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Introduction. Heat and moisture exchangers ("artificial noses"), provide *passive* airway humidification, and prevent intraoperative hypothermia in adults.[1] The efficacy of these filters has not been evaluated in infants and children, nor have they been compared to *active* humidification. Therefore, we compared central temperature, airway humidity, and recovery time in children given active, passive, or no respiratory gas humidification.

Methods. With approval from our Ethical Committee, we studied 27 children weighing 5-30 kg undergoing peripheral surgery lasting 1-3 h. Ambient temperatures were maintained at ≈ 22°C and a heating blanket, thermostatically-controlled at 37°C, was placed under each patient. Halothane/N_2O anesthesia was administered with a modified Ayre's t-piece. Fresh gas flow was calculated using the formula of Rose and Froese[2]; respiratory rate (≈ 30/min) and tidal volume (≈ 12 ml/kg) were adjusted to maintain an end-tidal PCO_2 near 35 mmHg. The patients were randomly assigned to *active* airway humidification and warming using a Fisher and Paykel® warmer set at 37°C (n = 10), *passive* airway humidification using the Humid-Vent® 1 heat and moisture exchanger (n = 8), or no airway humidification and heating (*control*, n = 9). Tympanic membrane temperatures were recorded every 10 min during surgery. Inspired relative humidity was measured using a Humidcap.® Rectal temperatures were recorded at 10-min intervals during recovery from anesthesia. Patients were released from the recovery area by an anesthesiologist who was unaware of the type of airway humidification used. Fitness for discharge was based on standard criteria which included rectal temperature ≥ 36°C. Differences between groups were determined using ANOVA and Student-Newman-Keuls tests; $P \leq 0.05$ was considered significant.

Results. Figure 1 shows that the relative humidity of the inspired gas was ≈ 90% in patients given active airway humidification and ≈ 30% in those given unconditioned gases. The heat and moisture exchanger increased airway humidity from ≈ 50% to ≈ 80% during the first 90 min of surgery; after 80 min of anesthesia, inspired humidity in these patients was not significantly different from those in the active group. Tympanic membrane temperatures increased in the patients given active airway humidification, remained relatively constant in those given passive humidification, and decreased in the control group. After 70 min of anesthesia, tympanic membrane temperature differences between each of the groups were significant. (fig. 2). Rectal temperatures increased ≈ 0.5°C/h following anesthesia and the duration of recovery (≈ 60 min) was not significantly different among the groups.

Discussion. The Humid-vent® 1 heat and moisture exchanger significantly increased airway humidification and, after 80 min of anesthesia, provided humidification similar to that provided by an active humidifier. Passive airway humidification prevented hypothermia whereas active humidification and heating increased central body temperature in these patients. Recovery was rapid in all patients and did not correlate with central temperature or type of humidification. It is likely that differences between the groups would have been greater in patients undergoing larger operations in colder operating rooms.

Supported in part by a grant from Gibeck Respiration, Inc.

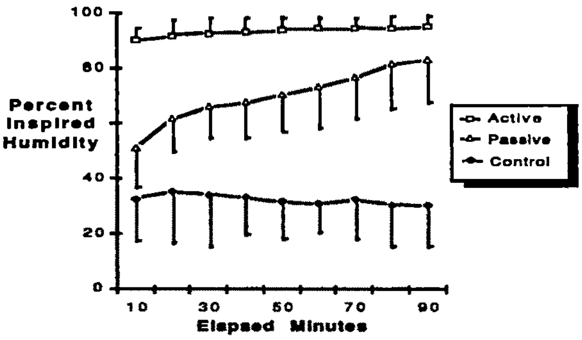

Figure 1. The mean inspired relative humidity (±SD) in 27 infants and children given active, passive, or no airway humidification. The humidity in the active and passive groups did not differ signficantly after 80 min of anesthesia. At other times, humidity in each of the groups differed signficantly.

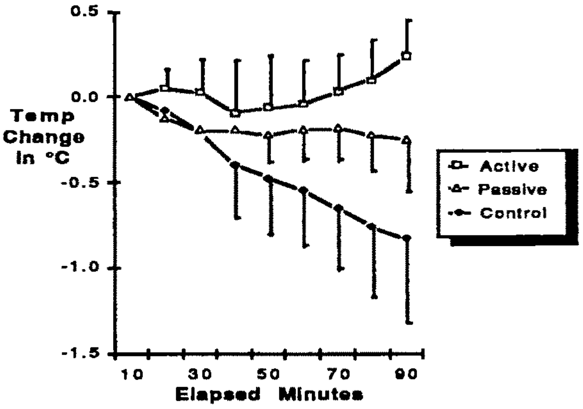

Figure 2. The mean change (±SD) in tympanic membrane temperature in 27 children receiving active, passive, or no airway humidification. After 70 min of anesthesia, temperature differences between each of the groups were significant.

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TITLE: TEMPERATURE MONITORING SITES IN INFANTS AND CHILDREN

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Introduction. Previous studies indicate that "central" (*e.g.*, tympanic membrane, esophageal, and rectal) temperatures are similar in anesthetized adults undergoing non-cardiac surgery.[1] We tested the hypothesis that the temperatures of these sites are similar in children undergoing non-cardiac surgery. We also tested the hypothesis that airway heating and humidification influences lower esophageal temperature.

Methods. With approval from our Ethical Committee, we studied 20 children weighing 5-30 kg undergoing peripheral surgery. Halothane/N_2O anesthesia was administered with a modified Ayre's t-piece. Fresh gas flow was calculated using the formula of Rose and Froese[2]; respiratory rate (≈ 30/min) and tidal volume (≈ 12 ml/kg) were adjusted to maintain an end-tidal PCO_2 near 35 mmHg. The patients were randomly assigned to *active* airway humidification and warming using a Fisher and Paykel warmer set at 37°C, *passive* airway humidification using the Humid-Vent 1 heat and moisture exchanger, or no airway humidification and heating (*control*). Tympanic membrane, esophageal, rectal, axillary, forearm, and fingertip temperatures were recorded every 10 min during surgery. The temperature of each measurement site was subtracted from tympanic membrane temperature and the results from each site at each time were averaged to determine temperature differences. Differences between groups was determined using ANOVA and Student-Newman-Keuls tests ($P \leq 0.05$ was considered significant).

Results. Figure 1 shows that esophageal, rectal, and axillary temperatures usually differed from tympanic membrane temperatures by < 0.2°C ($P > 0.05$). In contrast, the peripheral skin-surface temperatures were 1-3°C below tympanic membrane temperatures. Esophageal temperatures in patients receiving active and passive airway humidification were ≈ 0.25°C *higher* than tympanic temperatures whereas temperatures in patients without airway humidification were ≈ 0.25°C *below* tympanic temperatures ($P \leq 0.05$) (fig. 2).

Discussion. Esophageal, rectal, and axillary temperatures rarely differed from tympanic membrane temperatures by more than 0.2°C. This difference is small, compared with the physiological differences among individuals, and the decrease in temperature needed to trigger thermoregulatory responses in anesthetized humans.[3] Thus, any one of these temperatures identifies the bulk of central thermoregulatory input in children undergoing non-cardiac surgery. In contrast, forearm and fingertip skin-surface temperatures differed significantly from tympanic membrane temperature, indicating that skin-surface measurements are not a substitute for determining central temperatures. Esophageal temperatures were slightly, but significantly, increased when patients were ventilated with warmed and/or humidified respiratory gases.

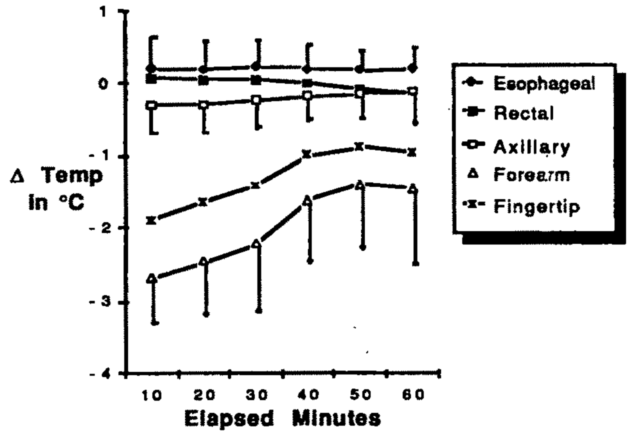

Figure 1. The mean difference between temperatures at five different measurement sites and tympanic membrane temperature in 20 infants and children. Vertical bars show the standard deviation of the mean. Tympanic, esophageal, rectal, and axillary temperatures did not differ significantly. Forearm and fingertip temperatures differed significantly from the "central" temperatures and from each other.

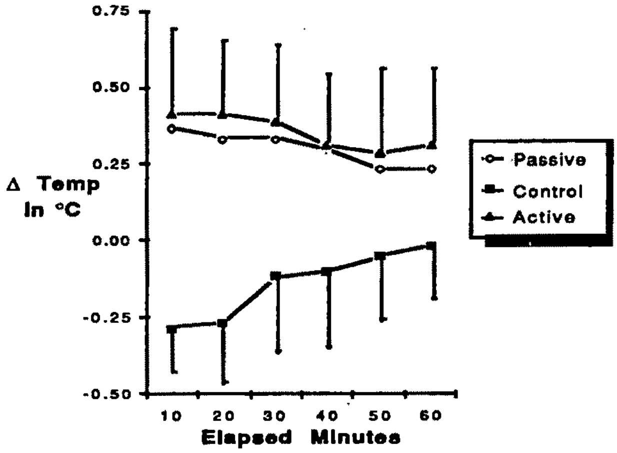

Figure 2. The average difference between esophageal temperature and tympanic membrane temperature in children receiving different airway humidification and/or heating. Vertical bars illustrate the standard deviation of the mean. Esophageal temperatures in the control group differed significantly from those of the groups given passive and active humidification.

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Title: **ATTENUATION OF ELECTROCONVULSIVE (ECT) AUTONOMIC HYPERACTIVITY BY ESMOLOL**

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Introduction The risk of adverse cardiovascular effects caused by the stress and sympathetic response from ECT (electroconvulsive therapy) has been previously documented[1]. As beta antagonists will modify the cardiovascular responses to sympathetic and catecholamine discharge, esmolol seems well suited to achieve this during ECT. Esmolol's properties as an ultra-short beta-1 receptor blocking agent were tested in a double-blind, randomized study of 40 matched pair trials, with each patient serving as their own controls.

Methods After institutional approval and informed consent, 10 ASA III adults requiring ECT were studied. 80 ECT cases were generated from these 10 patients. After insertion of an intravenous catheter, placebo or esmolol was infused for 4 minutes at 500 ug/kg/min and preoxygenation begun. At 4 minutes, anesthesia induction proceeded with 1 mg/kg of 1% methohexitol and 0.5 mg/kg succinylcholine IV. The electric stimulus was applied 90 seconds after succinylcholine administration and muscle relaxation was confirmed. The infused solution was decreased to 300 ug/kg-/min and continued until 3 minutes after electric shock and then discontinued. The parameters heart rate (HR, bpm) systolic (SAP, mm Hg), diastolic (DAP, mm Hg), and mean (MAP, mm Hg) arterial blood pressure were recorded every minute during infusion of placebo or esmolol for 15 minutes, and then every 5 minutes after the infusion was discontinued. Statistical comparison of the hemodynamic parameters for the 40 paired trials from the 10 patients was performed using the one-way repeated measures Analysis of Variance (ANOVA) tests. Comparison of maximum HR between the placebo and esmolol treatments was performed by the two-tailed paired T-test. To investigate changes from the start of infusion, the individual patient data was normalized by a percent change from baseline calculation such that the baseline for each patient was 0 ± 0%.

Results There were no differences in baseline hemodynamics nor in electroconvulsive stimuli under either placebo or esmolol treatment. Prior to shock and after 6 min of esmolol infusion, the percent change MAP was significantly lower compared to the placebo treated patients (Fig 1). Electroconvulsive stimulation occurred on the average 6.43 ± 0.49 min after infusion began. SAP and MAP were clinically (difference greater than 10%) and statistically ($P<0.05$) lower in the esmolol treated patients. From 3 to 9 min after infusion began, the esmolol treated patients had HR means that were significantly ($P<0.05$) lower compared to the placebo treated patients (Fig 2). Maximum HR was also significantly ($P<0.0001$) lower in the esmolol treated patients and this difference was large, 40 ± 19 bpm (Fig 3). The patients under esmolol treatment had a significantly ($P<0.01$) shorter seizure duration (60 ± 20 sec) as measured by the EEG than the patients under the placebo treatment (82 ± 30 sec). There were no adverse sequelae attributable to either ECT or esmolol therapy in this study.

Discussion The cardioprotective effect is well demonstrated in this double blind, randomized study. The experimental design using patients acting as their own controls through a series of ECT treatments decreased intra-patient variability. Esmolol blunted the blood pressure response but had its greatest effect on the maximum HR, decreasing it by 40 bpm. Esmolol did not lose its effect over several treatments and the infusion was found to be safe at the administered doses blunting adverse cardiovascular responses during ECT which may be of benefit to patients with cardiac disease.

Figure 1 COMPARISON OF MEAN PERCENT CHANGE MEAN ARTERIAL PRESSURE (% mm Hg)

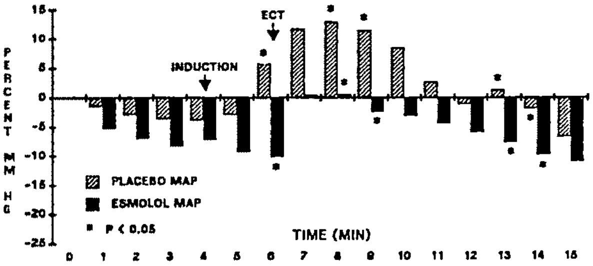


Figure 2 COMPARISON OF MEAN HEART RATES (bpm)

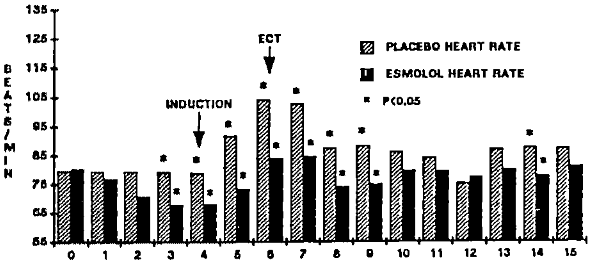
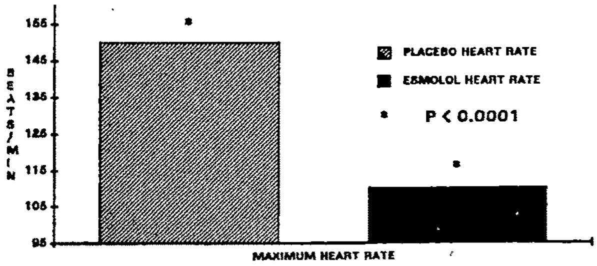


Figure 3 COMPARISON OF MAXIMUM HEART RATES (BEATS/MIN)



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Title: ESMOLOL AS PRIMARY AGENT FOR CONTROLLED HYPOTENSION

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Introduction. The use of controlled hypotension (CH) is a well established technique for limiting blood loss, reducing the need for transfusion, improving surgical conditions and shortening operating time associated with extensive orthopedic procedures, especially those involving the axial skeleton.[1] Esmolol (ES), a newer, extremely short-acting (β half life = 9 min), selective β1 blocking drug (Brevibloc, EI DuPont) has been used as an adjunct to nitroprusside (N) for CH in dogs[2] and for controlling hypertension in humans[3] but has not been employed as a primary agent for CH. The purpose of this study was to determine if ES could act as the primary agent for the production and maintenance of CH in patients undergoing elective procedures for scoliosis correction or instrumentation/fixation of traumatic back injury.

Methods. With IRB approval and as part of a larger study, 10 patients (ASA I-II), 12-32 yrs of age, scheduled to undergo posterior spinal fusion involving 7 or more thoracolumbar segments, were included in the study after written, informed consent was obtained. Pre-op medication included $0.004 mg \cdot kg^{-1}$ glycopyrrolate + $0.1 mg \cdot kg^{-1}$ morphine sulfate IM. Standard monitoring included somatosensory evoked potentials (SEP) of the posterior tibial nerves bilaterally, EtC02, Sa02 (pulse oximetry), urinary catheter, and radial artery pressure. Patients were infused with 500-1500ml of balanced crystalloid solution prior to induction to create a moderate diuresis, and continued at a rate sufficient to insure continued urine output at a rate greater than $0.5 ml \cdot kg^{-1} \cdot hr^{-1}$. Anesthesia was induced with thiopental, $4 mg \cdot kg^{-1}$, lidocaine, $1.5 mg \cdot kg^{-1}$, pancuronium, $0.1 mg \cdot kg^{-1}$ and sufentanil, $1 \mu g \cdot kg^{-1}$. Anesthesia was maintained with 0.25-0.37% isoflurane in oxygen, incremental doses of pancuronium, and a continuous infusion of sufentanil, $0.5 \mu g \cdot kg^{-1} \cdot hr^{-1}$, to maintain stable conditions for SEP monitoring. After positioning and prior to incision, ES was (pump) infused at a rate of $500 ug \cdot kg^{-1} \cdot min^{-1}$ until a 30% reduction in MAP was noted. 5-10 min were usually required for this response, after which the infusion rate was cut by half and usually half again, with MAP settling in the range of 55-60mmHg within 10-20 min of induction, at an infusion rate of $100\text{-}200 \mu g \cdot kg^{-1} \cdot min^{-1}$. Patients occasionally required boluses of ES ($1.0\text{-}1.2 mg \cdot kg$ was rapidly effective).[4] A wakeup test was utilized to confirm adequate motor function after surgical instrumentation, prior to closure in all patients.

Results. The study included 6 males and 4 females, 20 ± 7 yrs of age, weighing 58 ± 16 kg with fixation/fusion over 9.5 ± 2.8 vertebral levels. There were no significant changes in SEPs after either distraction or fixation in any patient. The procedures lasted from 164-313 min and averaged 234 ± 46 min. ES total dose was 3.6 ± 2.45gm at varying infusion rates over 220 ± 47 min. Pre-op Hct was 39.4 ± 6.1%.EBL was 725 ± 436ml ($3.1 \pm 1.6 ml \cdot min^{-1}$ or 1.4 ± 0.6ml per vertebrae fused per kg). Blood losses were replaced with 388 + 336ml PRBC; 6 of 10 patients received autologous blood. CH to a MAP of 55-60 mmHg was obtained within 10-20 min of surgical incision and maintained in this range (except for a 20 min period surrounding wakeup test) in all patients except one (a 14 yr old black female for scoliosis correction). In this patient, MAP was never less than 67 mmHg, even at ES infusion rates greater than $1300 ug \cdot kg^{-1} \cdot min^{-1}$. However, her blood loss was limited to less than $2.0 ml \cdot min^{-1}$.

Discussion. CH can limit intraoperative blood loss but has commonly been obtained with a mixture of intravenous and inhalational agents. Because of its rapid action and titratability, N has been used as primary agent for effecting CH in a wide variety of surgical procedures. However, because of its potential cyanide toxicity, reflex tachycardia, rebound hypertension, and tachyphylaxis, adjunctive agents (i.e., increased concentrations of inhalational agents, trimethaphan, propranolol, hydralazine, etc.) are commonly employed with N, to limit renal response and total dose requirement. In this study, with the exception of one patient, ES brought MAP within the desired range within 10-20 min of the beginning of the surgical procedure. Mean blood loss was not significantly different from that reported for a similar group of patients undergoing similar procedures (1.1 ± 0.3ml per level fused per kg) who were treated with N, propranolol and trimethaphan as necessary.[5]

The constraints of SEP monitoring (especially of the posterior tibial nerves) mandate a stable anesthetic which is maintained with a minimum of inhalational agents for optimal evoked activity in cortex.[6]

Within such limitations, and because of its titratability, rapid elimination and apparent lack of toxicity, we conclude that esmolol may be used safely and effectively as primary agent for the production and maintenance of controlled hypotension to limit blood loss, and facilitate SEP monitoring in extensive spinal surgical procedures.

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Title: NIFEDIPINE ATTENUATES THE ACUTE HEMODYNAMIC CHANGES THAT OCCUR WITH INTRAVENOUS DEXMEDETOMIDINE IN DOGS.

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Introduction: Alpha$_2$-adrenergic agonists have been shown to have anesthetic qualities. Dexmedetomidine (Farmos Group Ltd.) is a potent and selective alpha$_2$-adrenergic agonist. At doses sufficient to reduce anesthetic requirement (as measured by MAC) by over 90%[1,2] dexmedetomidine has been shown to significantly increase arterial blood pressure (MABP) and systemic vascular resistance (SVR) while reducing heart rate (HR) and cardiac output (CO) in dog. Theses effects are due to both peripheral alpha$_2$-adrenergic vasoconstriction and opposing baro-reflex meditated responses. Alpha$_2$-adrenergically mediated vasoconstriction is believed to be calcium mediated. In this study, the effects of nifedipine, a calcium channel blocker, were examined on the hemodynamic consequences of dexmedetomidine.

Methods: These studies were approved by the institutional Animal Research Committee. Isoflurane (ISO) anesthesia was induced by mask in 11 healthy unmedicated mongrel dogs, 13-22 kg. The dogs were intubated and allowed to breathe spontaneously at 1.5 - 2% ISO in oxygen, during the period of surgical preparation. All fluids and drugs were administered through a femoral vein catheter. Heart rate (HR), arterial (MAP), central venous, pulmonary arterial and left ventricular pressures (LVEDP and dP/dt) were recorded continuously on a direct writing polygraph. Cardiac outputs (CO) were determined in triplicate by thermodilution. Systemic vascular resistance (SVR) was calculated. End-tidal ISO and CO$_2$ concentrations were measured by mass spectrometry. Core temperature was maintained at 38 ± 1°C. Following a stabilization period of 30 min minimum alveolar concentration (MAC) of ISO was determined by published techniques and control hemodynamics values were recorded (control values). Dexmedetomidine (20 μg/kg) was administered over 2 min, after which the ISO was discontinued. Ten min after dexmedetomidine measurements were again recorded (dexmedetomidine values) following which, nifedipine 10 μg/kg bolus with 2.5 μg/kg infusion was given for 20 min (low nifedipine values). Nifedipine 20 μg/kg with 5 μg/kg was then given for the next 20 min (high nifedipine values). Recovery to 33% and 50% MAC was then determined and then MVP-1248 (a selective alpha$_2$-adrenergic antagonist) was given to reverse dexmedetomidine (MPV-1248 values). Five of the 11 dogs received only dexmedetomidine for a time control. Analysis of variance for repeated measure, Bonferroni t-test and Student's t-test were used for data evaluation.

Results: Bolus administration of dexmedetomidine, 20 μg/kg, resulted in significant decreases in HR and CO as well as significant increases in MAP, LVEDP and SVR. dP/dt was not affected. Nifedipine, low and high dose, caused MAP, CO and SVR to return to control values. LVEDP was reduced significantly ($p<0.001$) but remained higher than the control value. Dogs treated with dexmedetomidine only had a lower CO ($p<0.01$), HR ($p<0.001$) and a higher SVR ($p<0.01$) at all time points examined. Nifedipine had no effect on dexmedetomidine anesthetic sparing effects. MPV-1248 reversed all changes observed.

Discussion: Dexmedetomidine has been shown to have many anesthetic qualities including sedation/narcosis, analgesia and anxiolysis. Studies to date where low doses of dexmedetomidine were given i.v. to human volunteers have not demonstrated any significant changes in hemodynamics. Higher doses which produce >90% reduction in MAC do produce, in dog, increased MABP and SVR with a reduction in HR and CO. These hemodynamic changes were blocked by both doses of nifedipine examined while having no effect on the central anesthetic qualities of dexmedetomidine.

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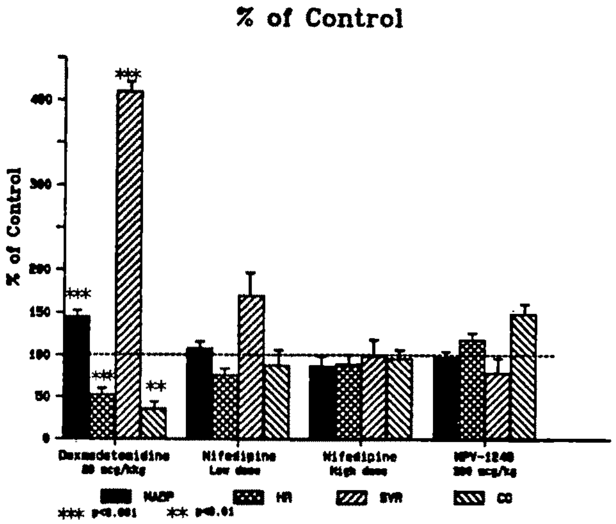

Title: RETURN OF COGNITIVE FUNCTION AFTER BRIEF ALFENTANIL ANESTHESIA: ANTIEMETIC PRETREATMENT AFFECTS RECOVERY

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Introduction: Alfentanil's rapid onset and short duration of action make it a useful drug for many outpatient procedures. One troublesome side effect of alfentanil and narcotic use, is a high incidence of nausea and vomiting which might result in increased costs and delayed patient discharge (1). Medications used to reduce post operative nausea and vomiting may prolong recovery of cognitive functions (2,3). Our ongoing study was designed to test for differences in return of cognitive function when patients were pretreated with several common modalities to prevent nausea and vomiting following alfentanil anesthesia.

Methods: 45 ASA Class I-II females age 23-40 scheduled for elective outpatient laparoscopy under general anesthesia gave their informed consent to participate in this IRB approved study. Patients were randomly assigned to one of four groups. Group 1 was given saline 15-30 minutes prior to induction. Group 2 received droperidol(D) 15 µg/kg intravenously, and Group 3 received metoclopramide(M) 150 µg/kg 15-30 minutes pre-induction. Group 4 was given the combination of metoclopramide and droperidol(D/M) I.V. Each patient received glycopyrrolate 0.2 mg IV before induction. The standardized anesthetic technique was vecuronium 0.01 mg/kg administered IV two minutes prior to induction, followed by alfentanil 20 µg/kg and succinylcholine 1.5 mg/kg to facilitate endotracheal intubation. Maintenance consisted of alfentanil 7 µg/kg and/or thiopental 0.3-1.0 mg/kg as needed in response to vital signs and movement. N_2O and O_2 was given in a 60-70/40-30 ratio. Muscle relaxation was provided with 0.01-0.05 mg/kg vecuronium and reversed after surgery with IV neostigmine 2.5 mg and glycopyrrolate 0.5 mg. All stomachs were suctioned prior to extubation.

A single blinded investigator administered a series of tests to all patients preoperatively and postoperatively at 30 minute intervals from arrival in the recovery room until discharge. Cognitive recovery, alertness, coordination and ocular divergence were judged utilizing Digit Substitution Test (DST), Trieger Dot Test (TDT) and Maddox Wing (MW). Patients rated their nausea on a linear analog scale. An average testing period lasted 3.5 minutes.

Comparison of groups and recovery values were analyzed by 3 way ANOVA with one repeated measure and chi square analysis. Results are presented as means ± S.D. The values for t_1 and t_5 (average 17 min and 139 min post surgery) were not included due to insufficient numbers of participating patients.

Results: There was no difference between the 4 groups in demographic data, duration of surgery (mean of 48.43 min) or dose of alfentanil administered (mean of 2531.8 µg). There was no difference found between the four groups in the incidence of nausea or vomiting postoperatively. The number of misses on the TDT was significantly elevated postoperatively compared to baseline in all medicated groups at t_2 ($p < 0.01$) (average 47 min). In those patients who received D the number of misses was significantly higher ($p < 0.01$ at t_2 and t_3 (average 76 min), and in those patients receiving the D/M combination the number of misses were significantly ($p < 0.05$) elevated at all times tested (Fig 1). The number of correct answers on the DST were significantly decreased in all groups at t_2 ($p < 0.01$). While the number of correct answers improved with time, they remained significantly ($p < 0.05$) depressed for the D and D/M groups at t_3 and t_4. The MW test demonstrated significant divergence in all medicated groups at t_2; the D group ($p < 0.05$) and D/M ($p < 0.01$) combination group remained significantly divergent throughout the study period.

Discussion: D and M both alone, and in combination, have been recommended for use to reduce nausea and vomiting following anesthesia (2,4). The data show that the use of D, especially in combination with M, is associated with delayed recovery of cognitive abilities as measured by the TDT and DST. In addition, similar to the cognitive function tests, the MW test demonstrated significant divergence when the combination of M and D is administered. It is apparent from this study that D prolongs recovery of cognitive functions after brief alfentanil anesthesia. The addition of M further delays recovery. While it is known that nausea and vomiting delays discharge, prophylactic anti-emetic treatment with these medications may of its own delay return of cognitive function.

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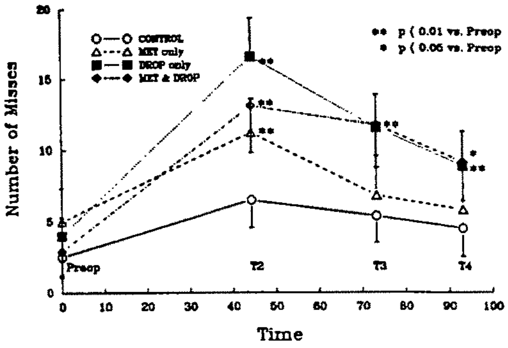
TRIEGER DOT TEST



TITLE: *HIGH DOSE NALBUPHINE (0.8 mg/kg) DURING BALANCED ANESTHESIA WILL NOT PRODUCE APNOEA*

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Introduction. Nalbuphine hydrochloride is an agonist-antagonist analgesic of the phenanthrene series. The aim of this study was to assess the effect on respiration of cumulative doses of nalbuphine in spontaneously breathing patients under anesthesia and to determine any correlation with plasma nalbuphine levels.

Method. Ten patients undergoing elective surgery participated in and gave written informed consent for this open study, approved by the hospital ethics committee. Pre-medication of oral diazepam, 0.15 mg/kg, was given 2 hours pre operatively. Anesthesia was induced with a sleep dose of thiopental and following succinylcholine 1 mg/kg, the trachea was intubated. The patient then breathed spontaneously, from a mapleson A circuit, a gas mixture of 67% N_2O in oxygen with 1% halothane, at a fresh gas flow of 100 mls/kg/min. Standard cardiovascular parameters were monitored non-invasively. Tidal volume and respiratory frequency were measured continuously by wet spiro- metry, and CO_2 concentration by capnography, this method having been previously validated in other studies[3]. Following achievement of a steady state of respiration, and prior to any surgical stimulation, an IV infusion of nalbuphine 0.2 mg/kg was delivered over 3 minutes (I). After 3 minutes, a further infusion of nalbuphine 0.2 mg/kg was administered over 3 minutes (II). Following a final 3 minute interval, nalbuphine 0.4 mg/kg was infused over 3 minutes (III). Blood samples, withdrawn during the steady state, 3 minutes after completion of each infusion, and 15 and 30 minutes after infusion III, were assayed for nalbuphine levels. Minute volume respiratory rate and PE CO_2 were derived from the continuous recordings. All patients were assessed post-operatively, and any side effects noted.

Results. The mean age of the patients was 29.2 years (SEM 2.6) and their mean weight, 63.9 kg (SEM 2.7). There were 8 females. Figure 1 shows the mean values for respiratory frequency indices at the indicated times. Statistically significant differences from steady state were found at I + 1min for respiratory frequency, and at all times for minute volume. PE CO_2 rose significantly from steady state at I + 4 min and remained at this level during subsequent infusion. The plasma nalbuphine levels showed an interesting correlation with respiratory parameters. All patients had uneventful emergence from anesthesia and satisfactory post-operative analgesia. A 70% incidence of nausea and vomiting was noted.

Discussion. Several workers have suggested that there is a ´plateau effect´ for respiratory depression with increasing doses of nalbuphine [1,2]. However, such studies have employed inaccurate methods for measurements of respiratory function. This study was undertaken in non-stimulated patients under balanced anesthesia and measuring respiratory parameters directly by accurate wet spirometry. The results show that 0.8 mg/kg nalbuphine causes respiratory depression which is limited and can be likened to a plateau effect. Apnoea was not produced in any patient during the period of study.

Under balanced anesthesia, high dose nalbuphine provides safe cardio-respiratory conditions and satisfactory analgesia.

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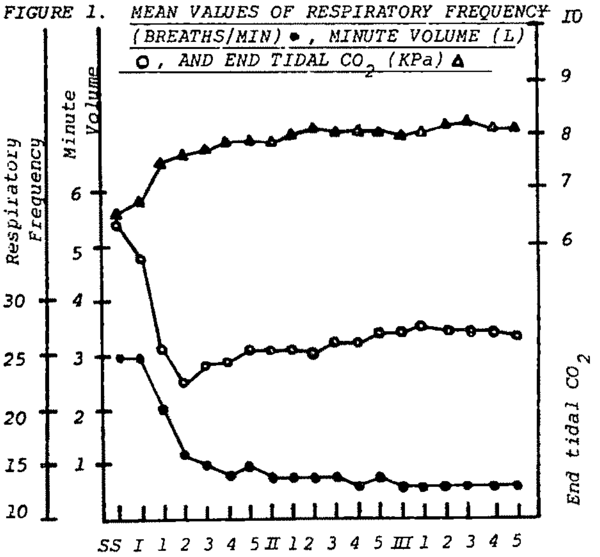
FIGURE 1. *MEAN VALUES OF RESPIRATORY FREQUENCY (BREATHS/MIN) ●, MINUTE VOLUME (L) ○, AND END TIDAL CO_2 (KPa) ▲*



TITLE: NEGATIVE INOTROPIC EFFECTS OF PROPOFOL VERSUS ETOMIDATE AND THIOPENTAL ON RABBIT PAPILLARY MUSCLE

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Introduction: Intravenous induction of anesthesia is frequently associated with significant decreases in blood pressure. However, clinical studies are conflicting with respect to the cardiac effects of the commonly used induction agents. In addition, comparative data regarding the direct myocardial depressant effects of these agents are not available. Therefore, we examined the effects of propofol (PRO), etomidate (ETOM) and thiopental (STP) on cardiac contractile function *in vitro* using a rabbit papillary muscle model.

Methods: This protocol was approved by the Institutional Animal Use and Care Committee. Male rabbits, 2-3 kg, were anesthetized with isoflurane in O_2 followed by thoracotomy and rapid cardiac excision. Suitable right ventricular papillary muscles were excised and placed in a bath containing Krebs-Henseleit buffer at 30°C bubbled with $95\%O_2/5\%CO_2$. The muscles were stimulated at a frequency of 0.3 Hz and allowed to equilibrate. Each muscle was then stretched to maximal tension and equilibrated for 60 min prior to baseline measurements of peak tension and maximum rate of tension development (dT/dt). Incremental additions were then made to the bath of either PRO (aqueous emulsion, n=7), ETOM (in ethanol, n=8) or STP (in saline, n=6) to produce final anesthetic concentrations of 10^{-6}, 10^{-5}, $3X10^{-5}$ and 10^{-4}M. Control muscle preparations were treated with incremental additions of vehicle (n=6). Each addition to the bath was followed by a 30 min equilibration period. Following the final dose (10^{-4}M) the bath was rapidly drained and replaced with fresh buffer ("washout"). Baseline values among the groups were compared using a one-way ANOVA. Responses to the anesthetic drugs were converted to percent of baseline and analyzed using a two-way ANOVA with repeated measures followed by one-way ANOVA and Bonferroni test to identify group differences at the various doses.

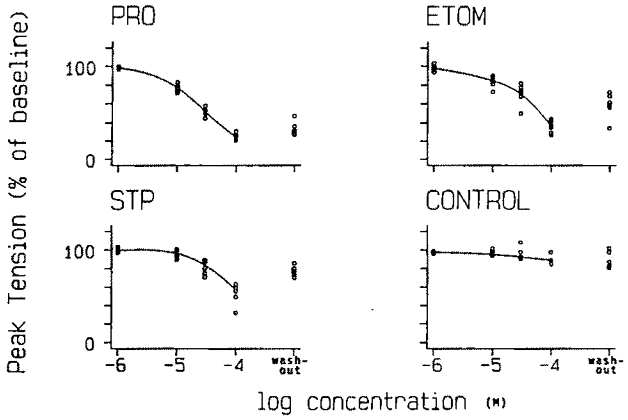
Results: There were no significant differences in the baseline data among the four groups. Preliminary studies indicated that the dose of ethanol vehicle added to the bath in the ETOM group had no effect on peak tension or dT/dt, and ethanol vehicle was subsequently used for the incremental additions in the control group. While there were no significant differences noted between groups at 10^{-6}M, at higher concentrations the anesthetic agents produced significant depression of peak tension compared to controls, $p<0.05$ (figure). In addition, the effects on peak tension were significantly different between the three drug treatment groups (PRO>ETOM>STP). At 10^{-4}M, the mean values (±S.E.M.) were 25±1%, 37±2%, 53±5%, and 91±2% of baseline for the PRO, ETOM, STP and control groups respectively. Following washout there were significant increases in myocardial function in the treatment groups. Similar results were obtained for the dT/dt data. Nonlinear regression analysis was used to calculate ED_{25} and ED_{50} values (table).

Discussion: Our results indicate that these three intravenous anesthetics produce dose-dependent direct myocardial depression. Considering the established anesthetic potency ratio of 1 : 7 : 0.5 for propofol: etomidate: thiopental, their relative cardiac depressant potencies at equianesthetic concentrations would be approximately 1 : 0.05 : 0.3. Since our data represent the response to unbound drug, consideration must also be given to the differences in protein binding between propofol (98%), etomidate (75%) and thiopental (86%). Thus, the predicted cardiac depressant potency ratio *in vivo* (at equianesthetic concentrations) is 1 : 0.6 : 2. These data suggest that the likelihood of direct cardiac depression following IV induction with these agents would be thiopental > propofol > etomidate. However, the peak unbound drug concentrations expected following IV induction with propofol (.1-.2 ug/ml, 0.5-1uM), etomidate (0.05-0.1 ug/ml, 2-4uM), and thiopental (3-7 ug/ml, 10-20 uM) are unlikely to produce direct cardiac depression in healthy patients. Thus, the differing effects of these drugs on blood pressure *in vivo* may be related more to differing effects on the peripheral vasculature and central cardiovascular reflexes. Nevertheless, increased cardiac sensitivity (e.g. in the elderly or patients with cardiac disease) or an increase in unbound drug concentration (e.g. decreased protein binding) could result in significant direct myocardial depression following intravenous induction of anesthesia with these agents.

TABLE:

	ED_{25}			ED_{50}		
	uM	(ug/ml)	potency	uM	(ug/ml)	potency
PRO	12	(2.1)	1.0	33	(5.9)	1.0
ETOM	24	(5.8)	.36	66	(16.1)	.36
STP	55	(14.5)	.14	158	(38.2)	.15

FIGURE:



Title: EFFICACY OF A SINGLE ORAL CYCLOSPORINE DOSE PRIOR TO LIVER TRANSPLANTATION

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Introduction. Cyclosporine (CYS) is a mainstay of immunotherapy for hepatic transplantation. It is generally given in our institution in a single oral preoperative dose, with the intention of providing a therapeutic CYS level at the time of graft reperfusion. While pharmacokinetics of chronic oral CYS has been fairly well described, it has not been determined whether a randomly timed preoperative dose results in desired blood levels. The present study attempts to relate time of preoperative CYS administration with levels attained during anesthesia and surgery.

Methods. Following approval of the Institutional Review Board and obtaining informed consents, twelve patients admitted for initial orthotopic liver transplantation were given CYS 10 mg/kg mixed in 6 oz. chocolate milk orally shortly after hospital arrival, 2-10 hrs preoperatively. After oral premedication with only diazepam 5-10mg, patients were brought to the operating room. Following rapid-sequence induction of anesthesia with thiopental, succinylcholine, and sufentanil, blood samples were drawn for CYS levels (Whole blood FPIA TDX, Abbott Labs, Chicago, IL). Anesthesia was maintained with sufentanil and isoflurane in air/02. Additional blood samples were drawn at two hours post-induction, and again at the time of reperfusion of the graft liver. Nasogastric evacuation was not done in 10 patients, and only after 1.5 hrs in two patients. Fluid and blood product administration was recorded for each time interval; veno-venous bypass was employed in all cases. Urine output was well maintained. All patients received intravenous CYS within the first 24 hours postoperatively and thereafter; any evidence of acute rejection was noted.

Results. As depicted in the accompanying table and figure, administration of CYS <4 hrs prior to anesthetic induction uniformly yielded levels <700 ng/ml at graft reperfusion. The minimum level considered therapeutic in our insititution is 700 ng/ml. In two cases, levels were >700 at induction and later declined. Four of five patients receiving CYS between 4-7 hours pre-induction had therapeutic levels at reperfusion. Patients had received a mean quantity of 241 ±337 ml of crystalloid at induction, and 0 ml blood products; 1800±1026 ml and 830±820 ml, respectively, at 2-hours post-induction; and 3442±1148 ml and 2350±820 ml at reperfusion, cumulatively. No episodes of regurgitation or aspiration occurred.

Discussion. Although CYS is normally described as having a peak serum concentration 2-4 hours after an oral dose[1], adequate levels were not seen in our patients unless more time had elapsed prior to anesthesia. Preoperative anxiety might have contributed to diminished induction levels. Reduced levels at 2-hours post-induction and reperfusion might be attributable to delayed gastric emptying, reduced gut blood flow, and/or direct effects of isoflurane on the gut itself. These effects were proposed in an animal study in which isoflurane impeded CYS absorption[2]. Also, the large fluid shifts seen during this operation may have had contributory dilutional effects which are difficult to quantify. Therapeutic CYS levels vary between institutions and assays; notably, the FPIA assay used here yields values that are approximately 80% of those given by whole-blood RIA assays in use elsewhere, and our results should be interpreted with these caveats.

Given these results and the theoretical risks associated with a large preanesthetic oral intake, CYS should be given orally no less than 4-5 or greater than 7 hours preoperatively.

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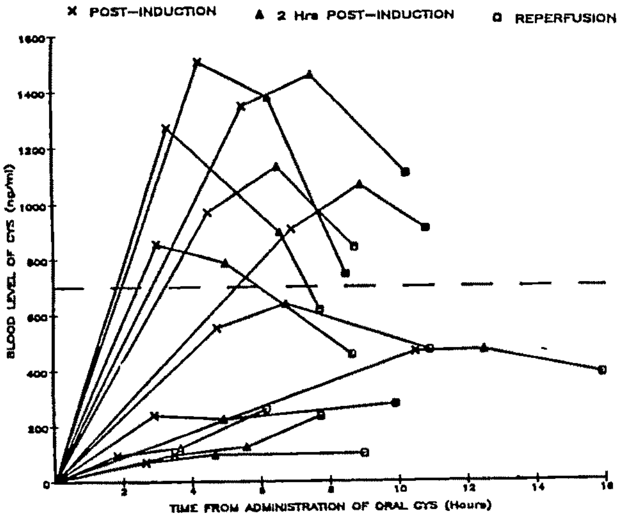
CYS Levels ng/ml at:	TIME ELAPSED BETWEEN CYS DOSE AND INDUCTION		
	< 4 hrs	4-7 hrs	> 7 hrs
INDUCTION	438 ± 505	1057 ± 377	468
2-Hr Post-Induction	376 ± 366	1135 ± 321	473
REPERFUSION	325 ± 183	816 ± 234	387
Patients with level >700 at REP (n)	0 / 6	4 / 5	0 / 1



Title: A PROSPECTIVE ANALYSIS OF UPPER EXTREMITY NEUROPATHY FOLLOWING HEPATIC TRANSPLANTATION

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INTRODUCTION: A high incidence (73%) of neurologic deficits has been reported in patients after hepatic transplantation[1]. This was determined by a retrospective study, the results of which are significantly higher than previously reported (0.89%)[2]. In order to further evaluate the incidence, onset and etiology of these upper extremity neuropathies, we designed this prospective study.

METHODS: Following approval by the institutional review board, informed consent was obtained from twenty six patients requiring liver transplantation. All patients were examined preoperatively and on the first and third postoperative days. Patients with preoperative neurologic deficits were excluded from the study. Meticulous attention was given to intraoperative positioning and padding of patients during the transplant.

These patients, when they were at least one month post transplant, were also sent the same questionnaire as that sent by Whitten et al[1]. They were specifically asked whether they had noticed any changes in sensation in the upper extremities since their transplant. The patients were also asked to illustrate, on a diagram of a human figure (anterior and posterior views), the exact distribution of any neurologic deficit(s).

We also determined the average cyclosporin levels in the first 30 days posttransplant, the peak cyclosporin level during the hospitalization and the number of days the patient's cyclosporin level was greater than 900 mcg/ml (levels above 900 mcg/ml are considered undesirable in our institution).

RESULTS: At the postoperative exam, 5 of 26 patients (19%) exhibited some degree of upper extremity neurologic deficit. The deficits were divided into three groups: a) specific nerve injury b) non specific nerve injury c) numbness limited to axillary incision (where surgical dissection for placement of the axillary cannula for veno-venous bypass was performed). Refer to Table 1.

Questionnaires were returned by 18 of 26 patients. Neurologic deficits were indicated by 13 of 18 respondents (72%). The deficits were categorized as above (Refer to Table 1).

There were no statistically significant differences in the cyclosporin levels measured in patients with or without neurologic deficits.

Discussion: The neurological evaluation on the first and third postoperative days revealed a 19% (5/26) incidence of upper extremity neurologic deficit. One patient had a specific ulnar nerve injury occurring at the level of the axilla where dissection for the veno-venous bypass cannula was performed. Another patient had symptoms of tingling in both arms and hands which has previously been attributed to cyclosporin neurotoxicity[3]. The remaining three patients had areas of numbness limited to axillary incision.

Upon reviewing these patients at one month or more post transplant by survey, it was discovered that the incidence of neurologic deficits had increased to 72%. This is similar to that reported by Whitten et al (73%)[1]. Specific nerve injuries developed in 4 additional patients after leaving the hospital, 2 involving the ulnar nerve and 2 involving the intercostobrachialis cutaneous nerve. The patients with ulnar nerve injury had negative immediate postoperative examinations. The other two patients only complained of incisional numbness immediately postoperatively, but this had progressed to become a specific nerve injury by the retrospective self evaluation.

Peripheral neuropathies that developed postoperatively may be the result of the neurotoxic effects of cyclosporin and high dose prednisone[3]. These neurotoxic effects may be aggravated by hypomagnesemia, renal impairment and hypotension[3]. The fact that there were no differences in cyclosporin levels in patients who reported neurologic deficits and those that did not, may illustrate that some patients may be more susceptible to the neurotoxic effects of cyclosporin than others.

The number of nonspecific nerve injuries had increased from one to seven patients at one month or more postoperatively. These deficits consisted of generalized bilateral upper extremity paresthesias, which has previously been attributed to cyclosporin neurotoxicity. This neurotoxicity may also delay nerve healing as two patients still reported incisional numbness in the postoperative survey.

CONCLUSION: The data presented here shows that the incidence of upper extremity neuropathy post hepatic transplant is significant.This incidence increases in the postoperative period. It appears that the continued and prolonged administration of cyclosporin has a neurotoxic effect on peripheral nerves. It may also potentiate and prolong any existing neurologic damage.

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TABLE 1.

	Postoperative Exam (n=26)	Response from Survey (n=18)
Specific Nerve Injury	1	4
Non Specific Nerve Injury	1	7
Incisional Numbness	3	2

Title: PLASMA CONCENTRATIONS OF MIVACURIUM CHLORIDE DURING INFUSION ADMINISTRATION IN CHILDREN ANESTHETIZED WITH HALOTHANE-NITROUS OXIDE OR NARCOTIC-NITROUS OXIDE

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Introduction. Following bolus administration of a neuromuscular blocking drug the observed effect depends on the kinetics of the drug as well as the sensitivity of the neuromuscular junction to the drug. During exposure to a continuous infusion of drug equilibrium between blood and effect compartment will develop. At this point the effect will be directly related to the plasma concentration of drug. The infusion rate (IR) required to maintain stable neuromuscular blockade will equal the clearance of drug (Cl) times the plasma concentration required to produce that degree of effect (CPSS) (1). This study was undertaken to measure the plasma concentration of mivacurium during infusion, stable neuromuscular blockade, and stable anesthetic background in children, and to use this information to estimate Cl of mivacurium.

Methods. Eighteen children (ASA status I-II) between 2 and 10 years old, having low risk elective surgical procedures were studied. The study was approved by the Human Rights Committee of the Children's Hospital of Pittsburgh; informed consent was obtained from a parent. No patient received aminoglycoside antibiotics or antihistamines within 48 hours of the study. For the nine patients in group one anesthesia was induced with nitrous oxide (70%), oxygen (30%) and halothane (up to 4% inspired). An intravenous catheter was placed and atropine (10 mg/kg) was given. Intubation was performed prior to administration of muscle relaxant. End-tidal halothane concentration was adjusted to 0.8 ± 0.05%; fentanyl (1-3 mg/kg) was given as needed. For the nine patients in group two preoperative medication included variable combinations of diazepam (0.1-0.2 mg/kg) PO, morphine (0.1-0.2 mg/kg) IM and methohexital (20-30 mg/kg) PR. Nitrous oxide was administered by mask, an intravenous catheter was placed, and thiopental (4-10 mg/kg), diazepam (0.1-0.2 mg/kg), and fentanyl (2-6 mg/kg) were given. Anesthesia was maintained with nitrous oxide (70%) and oxygen (30%) and fentanyl.

The ulnar nerve was stimulated supramaximally with repetitive trains-of-four stimuli (2 Hz for 2 sec at 10-sec intervals) at the wrist with surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan Bennett/Datex monitor. Blood was obtained for measurement of pseudocholinesterase activity (PA), dibucaine number (DN), and for baseline of the mivacurium assay. An IV bolus dose of mivacurium was administered; neuromuscular block and recovery were observed. A second bolus dose was then administered to establish 100% block. After recovery to 5% of baseline, an infusion of mivacurium (0.5 mg/ml in 5% dextrose) was begun at 10-20 mg/kg/min and titrated to maintain 89% to 99% neuromuscular blockade. The degree of neuromuscular block during infusion was expressed as percent of control in that the height of the first train-of-four response (T1) during infusion was compared with the control EMG height.

Fifteen minutes after the beginning of the mivacurium infusion, the initial blood specimen to be examined for mivacurium concentration was obtained. Two and one half mls of blood were drawn from a large intravenous catheter into a heparinized syringe. Within 20 seconds of the beginning of sampling, the blood was placed into a tube containing 0.2 ml of 0.25% phospholine iodide and EDTA (K3). Plasma was removed and frozen for later analysis. At intervals during continuous infusion up to four more additional specimens were obtained.

Mivacurium was extracted from plasma by solid phase extraction on a C-1 reversed-phase cartridge (Bond-Elut) with acidified methanol as the elution solvent. The extracts were analyzed by reversed-phase HPLC on a C-1 column (Spherisorb S5Cl) with UV detection at 210 nm. The mobile phase was 70% acetonitrile and a mixture of 30% phosphate buffer (pH 3) containing 10% methanol. The accuracy and precision of the method are approximately 90% and the sensitivity limit is 10 ng/ml.

Estimated Cl (ml/min/kg) was calculated by dividing the IR (mg/kg/min) by the CPSS (ng/ml) for each data point. Only sampling points where the IR of mivacurium had been constant for at least 5 minutes prior to plasma sampling were included in the analysis. Data are presented as $\bar{x}$ ± SE. T-test was used where appropriate with statistical significant accepted at $p \leq 0.05$.

Results. Plasma was obtained during stable infusion rates which produced between 91 and 98% blockade of the T_1 response. Preliminary analysis of the data suggest that the CPSS of mivacurium ranged between 132 and 486 ng/ml. Preliminary estimates of average Cl ranged from 36 to 79 ml/min/kg. Averaged data from individual patients are presented in Table 1. PA and DN were normal for all except one patient in group one, who therefore did not contribute data to Table 1. IR was 298 ± 29 µg/M^2/min in group one and 356 ± 33 µg/M^2/min in group two. This was not a statistically significant difference.

Table 1. Mivacurium Infusion Data ($\bar{X}$ ± SE)

Anesthetic Background	Mivacurium Concentration (ng/ml)	Estimated Clearance (ml/min/kg	Infusion Rate (µg/kg/min)	Neuromuscular Blockade (% depression)	Age (years)
ONE Halothane N=8	234 ± 27	47.6 ± 6.1	11.0 ± 1.3*	95 ± 0.4	7.1 ± 0/6**
TWO Narcotic N=9	263 ± 28	55.9 ± 2.6	14.3 ± 1.1*	95 ± 0.6	4.2 ± 0.6**

* statistically significant difference (one tailed)
* * statistically significant difference (two tailed)

Discussion. Although the expected potentiation of neuromuscular blockade by halothane was observed in this study (the IR [µg/kg/min] in group one was less than that in group two), this was not associated with a significant difference in the CPSS95 or the Cl of mivacurium. The significant difference in age between groups is important. Other studies have suggested that the CPSS of nondepolarizing blocker will not change with age in the range of 2-10 years, but there may be a difference in volume of distribution of neuromuscular blocking drug in this age range (2). If there were a difference in volume of distribution of mivacurium between groups one and two, it would result in a lower IR (µg/kg/min) in the older children. Indeed, the difference in IR between groups one and two is decreased by referencing IR to surface area rather than weight.

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Title: DOES PRE-OPERATIVE GASTRIC EMPTYING DECREASE THE RISK OF ACID ASPIRATION IN OBSTETRICAL ANESTHESIA? (A STUDY OF GASTRIC ACIDITY AND VOLUME AT EMERGENCY CESAREAN SECTION).

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Introduction. Aspiration of gastric contents is the most common anesthetic cause of maternal mortality. Various means to decrease this danger have been employed including the unpleasant procedure of pre-operative stomach emptying using a wide bore tube. The object of this study was to see if this technique decreases the total number of patients at risk of acid aspiration, as compared to intravenous ranitidine.

Methods. 183 healthy mothers between 18 and 38 years of age, and 36 to 42 weeks gestation were included in the study. Patients who had evidence of cardiopulmonary disease, hypertension, diabetes or gross obesity > 110kg, were excluded. Written informed consent was obtained and the study approved by the Ethics and Standards Committee of this Medical Faculty. Gastric emptying was performed pre-operatively in 63 patients and the tube removed prior to anesthetic induction. Thereafter 30 ml of 0.3M sodium citrate was administered per os and the time noted (Group 1). Another 60 patients (Group 2) received sodium citrate only, while 60 patients (Group 3) received in addition to sodium citrate, ranitidine 50 mg by slow (1 min) i.v. injection, 5 mins prior to induction of anesthesia. A standard general anesthetic technique was used. Each group of patients was subdivided into 6 groups A,B,C,D,E, and F. In Group A aspiration of gastric contents for pH and volume measurements was done at 15 - 20 min, in Group B at 1 hr, in Group C at 2 hr, in Group D at 2.5 hr, in Group E at 3 hr and in Group F at 3.5 hr. Gastric contents were sampled at the above times, measured volumes recorded and the pH measured with Merck indicator paper, results of which were standardised against a Beckman Instrument pH electrode. Volume and pH results were compared between groups using the Mann Whitney U-test, the number of "at risk" patients in each group were compared using the Fisher Exact test. Our definition of an "at risk" patient was one with an intragastric volume of > 25 ml and pH less than or equal to 3.5. A p value of < 0.05 was considered to be statistically significant.

Results. Data on maternal age, weight, gestation, parity and times of ingestion of sodium citrate and/or ranitidine to induction of anesthesia were similar in the three groups. The slow i.v. injection of ranitidine did not cause any adverse effects. The pH values were significantly higher in Group 1 than in Groups 2 and 3 ($p < 0.02$) at 15 - 20 min, but were significantly higher in Group 3 (ranitidine) at 2, 2.5 and 3 hrs than the other two groups and significantly higher in Group 3 than in Group 1 at 3.5 hr ($p < 0.02$). Measured volumes were significantly lower in Group 1 than in Groups 2 and 3 at 15 - 20 mins 1, 2 and 2.5 hr ($p < 0.05$). There was no statistically significant difference in volumes between Groups 2 and 3 at any time. No patients were found to be at risk in Group 3 at any time, whereas there were three patients considered to be "at risk" in Group 1 and four in Group 2. However, there was no statistical difference in the number of patients at risk in Groups 1 and 2 ($p = 0.35$), Groups 1 and 3 ($p = 0.13$) or Groups 2 and 3 ($p = 0.06$).

Discussion. Although the use of a stomach tube to decrease intragastric volume prior to general anesthesia is often recommended in the literature(1), we know of only one study that has examined the effects of this technique prior to emergency obstetric anesthesia(2). In this latter study a comparison was made between pre-operative gastric aspiration by stomach tube, and i.v. apomorphine. The results showed that both methods were equally effective in decreasing volume and that neither guaranteed an empty stomach. The study did not, however, examine the effects upon pH and used a control of non-obstetric patients presenting to elective surgery. Our results show that pre-operative gastric emptying decreased mean intragastric volumes prior to cesarean section but that this did not significantly decrease the number of patients at risk of acid aspiration. The gastric volume required to produce the acid aspiration syndrome has been questioned and may be much more than 25 mls(3). In view of the above and the unpleasantness of the procedure, routine pre-operative gastric aspiration by stomach tube in order to decrease the incidence of acid aspiration is not justified but should still be used following a recent meal. The use of i.v. ranitidine in addition to sodium citrate may be of value if given at least 1 hr preoperatively.

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Title: HYPERKALEMIA DURING MASSIVE BLOOD TRANSFUSION IN PEDIATRIC CRANIOFACIAL SURGERY.

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Introduction: It is stated that hyperkalemia complicates whole blood transfusion only if transfusion rates exceed a blood volume in 40 minutes[1] or if blood is administered at a rate>120 ml/min.[2] It is believed that hyperkalemia does not occur during massive transfusion with citrated Packed Blood Cells (cPRBCs) because the plasma volume per unit is small.[1] This assumes that the plasma potassium concentration [K^+] in this plasma fraction is small. We suspected that cPRBC's contain a significant K^+ load. We tested this hypothesis by 1) a prospective analysis of the K^+ content in cPRBC's and by 2) a retrospective chart review of children (ASA1) undergoing intraoperative exchange transfusion during major reconstructive craniofacial surgery.

Methods: The following study was undertaken with institutional approval. The [K^+] in 28 units of cPRBC's aged between 2 and 28 days was determined. The [K^+] in 1 ml samples taken from each unit was measured by flame photometry (IL 943 Automatic flame Photometer, Instrumentation Laboratory). K^+ content {K^+} was calculated such that {K^+} = [(1-Hct)• V_{cPRBC}• [K^+]] where the hematocrit (Hct) was measured from a well mixed 1-2 cc sample on a Coulter Counter (Model S-Plus IV) and the volume per unit of cPRBC (V_{cPRBC}) was determined from the weight of the unit (Sartorius L2200P Electronic Toploader Scale). Polynomial regression analysis and the coefficient of correlation (r) were used to describe the relationship between changes in [K^+], {K^+} and age. Thirty charts were reviewed. All children received a balanced anesthetic technique. The criteria for inclusion in the study were 1) a sampling frequency of arterial blood for pH, HCO_3^-, K^+, and Hct analysis every hour, 2) a minimum 5 recorded blood analyses, 3) intraoperative blood transfusion ≥ 1 blood volume and 4) hemodynamic stability. The hourly urine output was derived from the anesthetic record. In addition the hourly rate of blood transfusion was estimated. The age of the blood transfused was traced through the Blood Bank records. From our prospective analysis of cPRBC's an estimate of the K^+ load delivered during transfusion was made. Paired t-test analysis was done between the pre-peak and peak K^+ values. Statistical significance ($p<0.05$) was accepted.

Results: [K^+] in cPRBCs increased with age.(fig 1) The data was described by a second order polynomial $y=0.361+5.664x-0.098x^2$, $r=0.71, p=0.0001$. The {K^+} per unit cPRBC also increased with age (fig 2, table 1). This relationship was described with the second order polynomial $y=0.599+0.256x-0.0047x^2$, $r=0.77$, $p=0.0001$. Thirty charts were reviewed. Fifteen failed to meet the inclusion criteria. Four patients suffered an intraoperative cardiac arrest and were excluded from the study. Eleven charts (table 2) met the inclusion criteria. Ten patients had an easily identified acute increase in K^+ during the course of surgery. (fig 3) In 9 patients the K^+ was temporally related to blood transfusion. The mean increase in K^+ 1.39 ± 0.4 mEq/l. Paired t-test analysis of the pre-peak and peak K^+ was statistically significant at $p<0.0001$. The mean K^+ load in cPRBCs associated with an obvious spike in serum K^+ was 0.66 ± 0.51 mEq/kg delivered over 1 to 2 hours.

Discussion: The [K^+] and {K^+} in cPRBCs found in this study are in agreement with those of Michael et al[3] (table1). These concentrations are in excess of the widely quoted [K^+] of 18-26 mEq/l for cPRBCs[1]. In spite of the small plasma volume, cPRBCs contain a significant K^+ load. Nine out of ten children had an acute rise in K^+ during transfusion of cPRBCs supporting the notion that cPRBCs contain an K^+ load. Although no patients suffered an untoward event, the mean dose of K^+ at the time of the K^+ peak exceeds the recommended rate of infusion of intravenous KCL.

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TABLE 1 Potassium content per unit of cPRBCs (228 ml)

Age of blood	K^+ content/unit	Michael et al.[3]
<1 week	1.4 mEq	1.7 mEq
1-2 week	3.0 mEq	3.1 mEq
2-3 week	3.7 mEq	4.4 mEq
>3 week	4.3 mEq	

TABLE 2 Range of potassium values and blood volume loss on 11 patients undergoing cranio-facial surgery

Pat	Age (Yr)	Weight (Kg)	Diagnosis	Blood loss ($ml \cdot kg^{-1}$)	K^+ (mEq/l)
Br	8.0	20.0	Crouzon's disease	320.0	3.4-6.7
R	0.8	9.5	Apert's syndrome	127.5	3.6-5.9
Bs	0.6	6.0	Craniosystosis	85.0	3.1-4.3
N	1.5	11.0	Cranial dysplasia	80.0	3.9-5.2
Re	0.6	7.6	Crouzon's disease	170.0	3.0-4.2
S	1.5	8.5	Apert's syndrome	400.0	3.8-5.9
Cr	2.0	10.0	Apert's syndrome	640.0	3.8-5.9
Co	7.0	31.5	Pfieffer's syndrome	75.0	3.8-5.6
Bt	0.8	7.0	Apert's syndrome	212.5	4.3-6.0
K	3.0	17.0	Crouzon's disease	112.5	3.2-4.4
Rb	9.0	24.0	OrbNeurofibroplasia	75.0	3.2-5.1

Figure 1 [K^+] in cPRBCs vs age

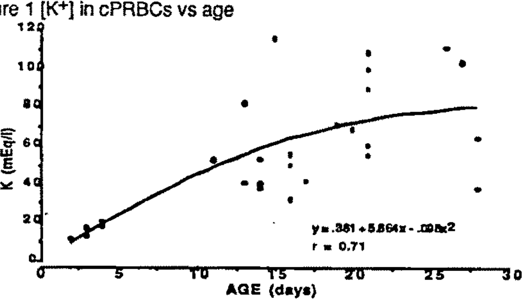


Figure 2 {K^+} in cPRBCs vs age

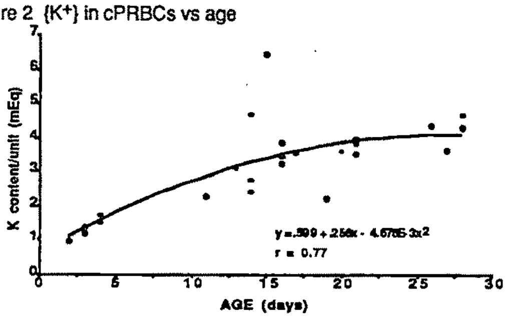
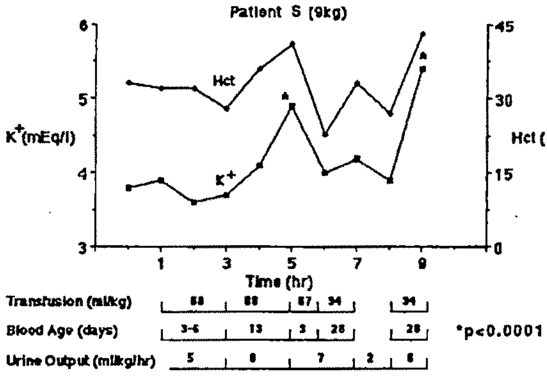


Figure 3 Representative trace of the intra-operative trend in K^+ and Hct.



Title: THROMBOELASTOGRAPHIC EVALUATION OF DESMOPRESSIN ACETATE FOLLOWING CARDIOPULMONARY BYPASS

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Introduction. Mediastinal bleeding due to hemostatic defects following cardiopulmonary bypass (CPB) occurs commonly, and desmopressin acetate (DDAVP) has been suggested as a useful agent in reducing blood loss[1,2], proposed mechanisms for which include increase in Factor VIII:von Willebrand factor (vWF) activity and amelioration of platelet dysfunction.[3] The thromboelastograph (TEG) is a valuable, real-time aid in the evaluation of coagulation, and is sensitive to alterations in platelet quantity and function, presence of clotting factors, as well as other parameters[4]; it may also better predict postoperative bleeding than can the activated clotting time (ACT) or laboratory coagulation profiles (CPRO)[5]. We herein evaluate the efficacy of DDAVP in hemostasis after CPB in routine coronary bypass graft procedures (CABG), utilizing the TEG alongside more traditional measures of coagulation.

Methods. Following approval of the Institutional Review Board, patients scheduled to undergo elective CABG (n=20) by either of two preselected surgeons were randomized in double-blind fashion to receive either desmopressin acetate (DDAVP) 0.3 mcg/kg IV, or saline IV placebo, following heparin reversal after CPB. One patient was excluded because of equipment malfunction. All patients had baseline TEGs (Hellige), ACTs, and CPROs (Hct, PT, PTT, fibrinogen, platelet count) performed following induction of anesthesia, and then again at these times: (1) post-protamine reversal of heparin, pre-DDAVP/placebo, (2) 15 mins post-DDAVP/placebo, and (3) 1-2 hr after arrival in ICU. Anesthetic technique was standardized, use of blood products perioperatively was recorded, and careful assessment of post-CPB intraoperative and first-ICU-day blood loss was made. A membrane oxygenator was used in all cases, and where the cell-saver was used, salvaged blood was retransfused prior to protamine dosing. Standard TEG-derived coagulation parameters were calculated in a previously described manner[4], and all results were analyzed with 1 or 2-sample t-tests.

Results. There were no significant differences shown between the DDAVP group (n=10) and the placebo group (n=9) either preoperatively, post-protamine, or post-DDAVP/placebo infusion by any measure of coagulation (TEG parameters, ACT, CPROs). Neither were differences significant between groups in post-CPB intraoperative and first-ICU-day blood loss, or in blood product usage. The post-operative PTT was significantly lower in the DDAVP group, but all other coagulation measures (including TEG) failed to show differences. Selected data are summarized below. No patient showed evidence of fibrinolysis (a reported complication of DDAVP), to which the TEG is extremely sensitive. No reoperations for hemorrhage occurred.

Discussion. In contrast to data derived from repeat or more complex operations[1,2], this series of uncomplicated CABGs showed no significant advantage discernable from the usage of DDAVP, even when a more sensitive assay of coagulation (TEG) was used. This may well be attributable to a relative reduction in hemostatic defects consonant with a simpler and more rapid surgery; of note, the mean 350 cc requirement for RBCs is much less than in many such studies. Our finding of shortened postoperative PTT has previously been seen[6], and may reflect DDAVP effects on activity of Factor VIII:c or vWF monomers.

The approximate patient cost of DDAVP therapy in our institution for a 70 kg patient is $180, and the potential for adverse drug effects exists. These, alongside our results, suggest that routine use of DDAVP in CABG is unwarranted.

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	Post-CPB EBL,cc	First 24° ICU EBL,cc	RBCs given in ICU, cc	Preop Hct,%
DD	395±248	879±353	315±563	38.4±5.6
PL	300±215	803±405	351±540	37.8±4.1

	Postop PT,sec	Postop PTT,sec	Postop plts,000	Postop Hct, %
DD	14.3±1.0	31.1±3.2*	203.8±71.9	32.2±5.1
PL	14.2±1.0	36.5±5.9	172.6±34.9	29.2±6.2

POSTOP TEG PARAMETERS

	R, min	R+K, min	MA, mm	Angle, deg
DD	5.3±4.4	13.7±6.9	23.8±2.5	40.7±10.0
PL	6.1±4.2	15.6±10.8	24.1±2.4	40.7±14.4

* p = 0.03. All other differences not significant.

Key: DD = DDAVP treated group, PL = placebo; plts = platelets, Hct = hematocrit, EBL = estimated blood loss, RBCs = packed red blood cells

Title: COMPARISON OF ZONES OF DIFFERENTIAL BLOCKADE OF LIGHT TOUCH, TEMPERATURE DISCRIMINATION AND PINPRICK SENSATION DURING ONSET, MAINTENANCE, AND REGRESSION OF SPINAL ANESTHESIA WITH HYPERBARIC TETRACAINE OR BUPIVACAINE

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Introduction. Spinal anesthesia is associated with zones of differential nerve blockade[1]. Bupivacaine and tetracaine, long-acting local anesthetics commonly used for spinal anesthesia, have not been compared with regard to their zones of differential blockade. These differential zones during onset, maintenance and regression of spinal anesthesia determine both perioperative patient comfort, as well as physiologic, especially vascular, changes. Therefore, we undertook a prospective, double-blind study to define the presence, duration, and extent of zones of differential blockade during clinical spinal anesthesia, the relation of the differential blockade zones to the local anesthetics used, and cardiovascular effects as reflected by blood pressure and heart rate.

Methods. Following approval by the institutional Human Investigation Committee, 51 patients scheduled to receive spinal anesthesia for elective surgery were randomly assigned to receive hyperbaric bupivacaine or hyperbaric tetracaine. Perioperative benzodiazepines were given in doses adequate for anxiolysis, without producing undue sedation, and perioperative narcotics were limited to a maximum of 2 ug/kg of feutanyl or its equivalent. All sensory responses were measured by the same anesthesiologist, who was blinded to the local anesthetic used, and who did not participate in any aspect of perioperative patient management.

The dermatomal levels of blockade of light touch (LT) temperature (T) and pinprick (PP) discrimination, as well as blood pressure (BP) and heart rate (HR) were measured 5, 10, 15, 30 and then every 30 minutes, until LT level regressed to the T_{12} dermatome[2]. The most craniad extension of sensory denervation was determined by each patient by comparing sensory stimuli applied to an unanesthetized area (e.g., shoulder tip) to the trunk in the mid-clavicular line. The level caudad to the lowest dermatome at which the sensory stimulus felt the same as at the shoulder tip, was considered the most cephalad level of blockade of the sensory modality being tested.

LT was measured by applying the dull, hinged end of a sterile safety pin to the skin without indenting it. T was measured by spraying the skin with a non-toxic, non-flammable, highly-volatile mixture of dichlorofluoromethane and trichloromonofluoromethane (Fluori-Methane, Gebauer). PP was measured using the sharp tip of a sterile safety pin protruding 3 mm beyond a rubber stopper. BP was measured using an automated sphygmomanometer, and HR was determined by electrocardiogram (ECG).

Data were analyzed as follows: 1) Continuous variables were analyzed using analysis of variance (ANOVA), with p values < 0.05 considered statistically significant. 2) Discrete variables were analyzed using chi-square tests, with p values <0.05 considered statistically significant. Data are presented as mean values ± SD.

Results. Of the 51 patients in this study, 29 were given bupivacaine and 22, tetracaine. The two groups were not statistically different with regard to sex, ASA physical status, age, weight, height, or dose (if 1 mg of bupivacaine in 8.25% dextrose and 1 mg of tetracaine in 10% dextrose are considered equipotent) of local anesthetic used. There were no statistically significant differences between the 29 patients who received bupivacaine and the 22 patients who received tetracaine with regard to the maximal spread of sensory denervation, at equipotent local anesthetic dosages (Table). The widths of the zones of differential blockade were also not statistically different between the 2 groups at any of the times measured, with the exception that light touch-to-pinprick and light touch-to-temperature zones were greater with bupivacaine than with tetracaine at 30 minutes from subarachnoid injection. The width of the differential blockade zones remained statistically and clinically unchanged within each of the groups during onset, maintenance and regression of spinal anesthesia. Finally, both blood pressure and heart rate, as well as intraoperative blood pressure and heart rate changes, remained similar with both bupivacaine and tetracaine.

DISCUSSION. One of the findings of the present study not previously quantitated, is that there was no statistically significant difference in the constancy of the zones of differential blockade during onset, maintenance, and regression of spinal anesthesia with either tetracaine or bupivacaine.

There were no statistically significant differences between the two groups in the mean maximal (e.g., most rostral) level of sensory denervation, and since there were also no significant differences in the extent of sympathetic denervation as a function of the local anesthetic used, it is thus not surprising that there was no statistically significant change in heart rate and blood pressure related to the local anesthetic used.

In summary, this study shows that at equivalent doses, hyperbaric spinal bupivacaine and tetracaine are very similar with respect to mean maximal rostral spread, that the zones of differential blockade to light touch, pinprick, and temperature modalities are statistically similar during onset, maintenance, and regression of spinal anesthesia, and that the choice of local anesthetic does not influence hemodynamic parameters.

TABLE

	LT	PP	T
Tetracaine	5.52 ± 1.99	4.14 ± 1.36	3.24 ± 1.72
Bupivacaine	6.76 ± 2.71	4.62 ± 1.85	3.55 ± 2.04

Maximal thoracic dermatome denervation level (Mean ± SD, $p < 0.05$).

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Title: DEEP HYPOTHERMIC CIRCULATORY ARREST, ANTERIOR FONTANEL PRESSURE AND VISUAL EVOKED POTENTIALS IN INFANTS

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Introduction: It has previously been demonstrated that a significant rise in anterior fontanel pressure (AFP) associated with a decrease in cerebral perfusion pressure occurs during the resumption of cardiopulmonary bypass (CPB) in infants after a period of deep hypothermic circulatory arrest (DHCA).[1] This increase in AFP has been attributed to a transient luxury perfusion state after DHCA. More recently, it has been shown that cerebral blood flow (CBF) is reduced during this initial period of rewarming CPB.[2] The relationship between cerebral function, AFP and CPB immediately post-DHCA in infants has not been previously described. As visual evoked potentials (VEPS) are a sensitive means of assessing cerebral function, we measured VEPS during the repair of congenital heart lesions in infants and correlated these with the period of increased AFP.

Methods: Following approval by the Human Studies Review Committee, 5 infants less than 8 months of age undergoing repair of congenital heart lesions with DHCA were studied. After induction of anesthesia and the establishment of routine monitoring, the Ladd transducer was fixed to the anterior fontanel using a previously described technique.[1] VEPS were recorded using a Nicolet CA-1000 from Oz to Fz. EEG was in response to binocular stimulation using LED goggles at a rate of 0.9/second. The amplifier gain was 10k and the filtering bandpass was 1-1000 Hz. Sixty-four artefact-free trials were included in each average. Baseline VEPS were collected at normothermia after anesthetic induction, and throughout the surgical procedure (cooling and warming bypass, post-bypass); postoperative VEPS were obtained approximately one week following surgery. Mean arterial pressure (MAP), AFP, VEPS, temperature (rectal/esophageal) and arterial blood gases were recorded post-induction, during cooling bypass, rewarming bypass and post-bypass. The times required for AFP to return to post-induction baseline after the period of DHCA and for return of VEPS were measured.

Data were compared using repeated measures analysis of variance and paired Student's t-test with Bonferroni correction for multiple comparisons. Statistical significance was accepted as $p < 0.05$. Values represent mean ± SD.

Results: The patients mean age was 4.4 ± 2.4 months and mean weight was 5.97 ± 1.9 kg. Indications for surgery included ventricular septal defect, atrioventricular septal defect, transposition of the great vessels and truncus arteriosus. Anesthesia was maintained with fentanyl or morphine and pancuronium. Duration of circulatory arrest was 51.6 ± 18.7 minutes with temperatures of 18.2 ± 2.5°C rectal and 10 ± 1.3°C esophageal. VEPS were no longer recordable at an esophageal temperature of 19.89 ± 3.9°C. VEPS were present again at 36.3 ± 0.76°C and normalized over a period of 31.6 ± 12.7 minutes. Table 1 shows values recorded for MAP, AFP, CPP and $PaCO_2$ (Stat). The mean time for AFP to return to baseline levels after DHCA was 23.9 ± 10.9 minutes and for the return of VEPS was 23.4 ± 11.5 minutes (p = NS) (Figure).

Discussion: Our data demonstrate that the return of VEPS following DHCA is related to the period of increased AFP. This suggests that there may not be an excess of flow over metabolic requirements in the period immediately following circulatory arrest as previously suggested.[1] Although this is contrary to the concept of luxury perfusion during CPB, it is in agreement with the work of others demonstrating a decrease in CBF following DHCA.[2] Such a reported decrease in CBF is compatible with the demonstrated decrease in CPP in our study and suggests a period of cerebral ischemia of greater duration than the period of DHCA.

References:

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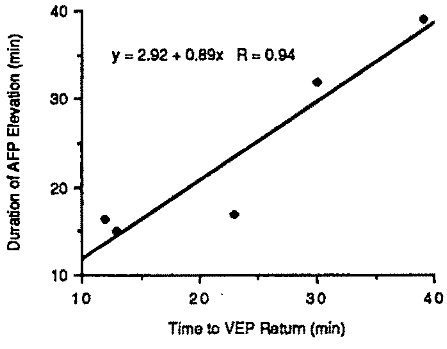
TABLE

	MAP (mm Hg)	AFP (mm Hg)	CPP (mm Hg)	$PaCO_2$ (mm Hg)
Pre-CPB	47.2 ± 5.9	9.0 ± 3.2	37.4 ± 4.9	33.0 ± 3.7
Cooling-CPB	36.8 ± 12.1⁺	9.2 ± 4.1	27.0 ± 8.7	33.8 ± 5.6
Warming-CPB	33.4 ± 10.0*⁺	17.0 ± 3.0*	17.6 ± 6.5°	35.0 ± 6.8
Post-CPB	55.8 ± 9.8	8.0 ± 2.4	44.2 ± 8.2	31.0 ± 4.2

*$p < 0.05$ compared to pre-CPB
⁺$p < 0.05$ compared to post-CPB
°$p < 0.05$ compared to pre-, cooling- and post-CPB



FIGURE

Title: INTRATHECAL MORPHINE FOR POST THORACOTOMY PAIN RELIEF IN CHILDREN

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Introduction. Intrathecal and epidural opiates have gained much popularity for postoperative analgesia. Their use in the adult population has been studied extensively and appropriate dosing regimens as well as complications have been documented (1). However use of intrathecal and epidural opiates for postoperative pediatric pain remains poorly elucidated. This preliminary study was designed to define appropriate doses, advantages and adverse effects of intrathecal morphine (ITM) in a group of pediatric patients undergoing thoracotomy.

Methods. This retrospective review of 16 pediatric patients who underwent elective intrathoracic procedures at the University of Missouri Hospital from 1985-1988 was approved by our institutional review board. These patients either received ITM or nalbuphine intravenously for pain control. Data was collected by a detailed chart review of hospital records. Statistical analysis utilized t-test.

Results. The 16 patients in the study were equally divided into two groups, Group I consisted of patients receiving ITM (Duramorph ^{R}), Group II consisted of patients receiving intravenous nalbuphine (Nubain ^{R}).

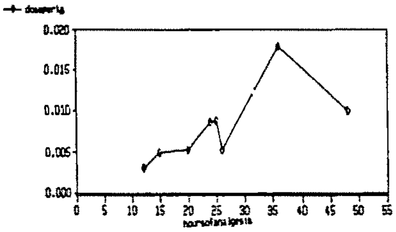
Agent Used: Duramorph

Patient	Age	Ht	Wt/Kg
1	12	151	31
2	5	112	17
3	7	112	19
4	7	127	19
5	6	116	20
6	7	131	25
7	3.5	98	16
8	9	109	21
Avg	7.1	119.5	21

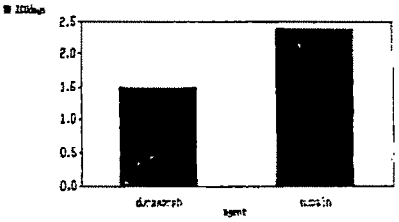
Agent Used: Nubain

Patient	Age	Ht	Wt/Kg
9	10	147	33
10	4	136	34
11	4	103	17
12	5	110	20
13	2	112	18
14	5	113	21
15	4	107	20
16	4	135	27
Avg	4.8	120.575	23.75

Computer generated graphics suggest a dose response curve for ITM in which higher doses 0.01-0.017 mg/kg are associated with longer duration of pain relief.



Although no difference was noted between the two groups with respect to total hospital stay, intensive care unit stays were significantly shorter in the intrathecal morphine group (at the 0.85% level).



With respect to complications, both nausea and/or vomiting (N/V) and urinary retention (URI) were significantly more frequent in Group I than in Group II (at the 0.95% level). On the other hand, patients in Group II were noted to have atelectasis more frequently. This observation was statistically significant (at the 0.95% level).

Agent Used: Duramorph

Patient	Dose	N/V	URI	PRU	RES	ATL
1	0.0087	1	1	0	0	0
2	0.0088	0	1	0	0	1
3	0.0053	1	1	0	0	0
4	0.0053	1	0	0	0	0
5	0.0100	0	1	1	0	0
6	0.0050	1	1	0	0	1
7	0.0031	1	1	0	0	0
8	0.0179	1	1	0	0	0
	Sum	6	7	1	0	2

Agent Used: Nubain

Patient	Dose	N/V	URI	PRU	RES	ATL
9	0.0000	1	1	1	0	1
10	0.0000	0	0	0	0	0
11	0.0000	0	0	0	0	1
12	0.0000	0	0	0	0	0
13	0.0000	0	0	0	0	1
14	0.0000	1	0	0	0	1
15	0.0000	0	0	0	0	1
16	0.0000	0	0	0	0	1
	Sum	2	1	1	0	6

Discussion. Those who anesthetize and operate upon children are always gratified when this can be accomplished with minimal physiologic and psychologic distress to their small patients. Early work by Jones et al (2) suggested this could be accomplished with intrathecal morphine. We have been pleased with this technique in our own practice. Jones et al (2) used a dose 0.02-0.03 mg/kg but suggested smaller doses may be equally effective. At our institution, we commonly employ a dose range of 0.005-0.02 mg/kg. It is interesting that our retrospective data suggest a dose response curve with higher doses being associated with longer duration. This has been suggested in adults with epidural morphine (3). Respiratory depression a dreaded complication with this technique was not seen in our patients. It has been suggested that this complication is also dose related (1,3). N/V and URI were common in our ITM patients but these complications were minimally distressing and easily controlled with a naloxone infusion as previously suggested (1). The significantly fewer cases of postoperative atelectasis in the ITM group suggests again (3) improved pulmonary function with these techniques. Although no effect on hospital stay has been shown here, it is gratifying to note a decrease in total intensive care unit stays. A prospective study looking at these issues is currently underway.

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Title: COOLING LIDOCAINE FROM ROOM TEMPERATURE TO 5°C NEITHER HASTENS NOR IMPROVES MEDIAN NERVE BLOCK

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Introduction. Cooling mammalian nerves in vitro slows conduction velocity and increases susceptibility to local anesthetic inhibition (1,2,3). Moreover, cooling lidocaine increases its pK_a as well as the relative amount of the protonated (active) form within lipid (4,5). We tested whether cooling lidocaine prior to injection speeds the onset or improves the quality of median nerve block.

Methods. Following approval of our protocol by the Institutional Review Board, 10 consenting adult volunteers of both sexes underwent serial recordings of motor and sensory nerve compound action potentials (CAPs), galvanic skin potentials (GSPs), and skin temperature. Temperature sensibility was assessed with aluminum cylinders cooled to 5°C or heated to 60°C. Pinprick sensibility was also tested. Subjects were excluded if they were pregnant or showed evidence of median nerve dysfunction.

Following baseline data recording, 5 ml of 1% lidocaine solution at either room temperature (RT) or 5°C (5C) was injected near the median nerve at the wrist. When paresthesiae were elicited, the needle was repositioned. Measurements were repeated at 1-min intervals until steady state conditions were reached. Dominant and non-dominant hands were studied in either order; likewise, RT and 5C lidocaine were administered in either order. Statistical comparisons were made using student's paired t-test. $P < 0.05$ was considered significant.

Results. Of 19 studies in 10 patients, 4 were discarded for technical reasons. Table 1 depicts the time required for half-maximal effects to be produced by RT or 5C lidocaine. Table 2 depicts the time delay between injection and the first perceptible signs of sensory loss. There were no significant differences between RT and 5C lidocaine. Thus, RT and 5C lidocaine developed electrophysiological and clinical signs of anesthesia at the same rate and produced comparable levels of block at steady state.

Discussion. We were unable to demonstrate any improvement in either rate of onset or completeness of block of any median nerve fiber type (Aα, Aδ or C) when we cooled lidocaine prior to injection, despite the well-known effectiveness of cooling of extremities as an anesthetic procedure, and despite previous studies showing potentiation of local anesthetic action by hypothermia (1,2,3). In most cases, at both RT and 5C, incomplete block of sensory function lagged far behind complete block of motor CAPs.

We studied a nerve block technique requiring small volumes of anesthetic. Our inability to show an effect of cooling may reflect rapid warming of the lidocaine by the surrounding tissue, preventing the nerve itself from being cooled. Such temperature buffering might not occur in a technique requiring larger volumes of anesthetic (e.g., brachial nerve plexus block). However, accidental intravenous injection of ice-cold anesthetic solution might produce severe cardiac toxicity.

We conclude it is unlikely that cooling of local anesthetics prior to injection will prove beneficial in clinical regional anesthesia.

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TABLE 1: TIME (MIN) TO PRODUCE HALF-MAXIMAL LIDOCAINE EFFECTS

	RT (n=8)	5C (n=7)
Motor CAP	8.7 ± 4.4	8.1 ± 3.7
Sensory CAP	10.3 ± 5.5	10.1 ± 2.4
GSP	8.6 ± 5.7	5.4 ± 3.5
Skin Temp.	15.7 ± 9.0	12.5 ± 4.2

TABLE 2: TIME (MIN) TO PRODUCE PERCEPTIBLE INHIBITION OF THE INDICATED SENSORY MODALITY

	RT (n=8)	5C (n=7)
Cold	6.6 ± 3.2	6.8 ± 4.5
Warm	5.4 ± 3.2	7.7 ± 3.0
Pin	6.1 ± 3.9	6.1 ± 3.9

All data reported as means ± standard deviations.

Title: INHALATIONAL ANESTHESIA DOES NOT ALTER THE EFFECT OF NITROGLYCERIN ON ARTERIAL OXYGEN CONTENT

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Introduction. Although intravenous nitroglycerin (GTN) and inhalational anesthetics can lower P_aO_2, the risk of potentiation is unknown. Because we frequently use GTN before and during cardiovascular surgery, we designed this study to determine the combined effects of these drugs on P_aO_2 and arterial oxygen content (C_aO_2).

Methods. With approval from our committee on human experimentation and informed consent from each patient, we studied 30 adults scheduled for elective abdominal or femoral vascular surgery. During the night prior to study, patients received 100-150 ml/hr of intravenous fluid. 0.10-0.15 mg/kg of diazepam was given orally at 05:00 and 0.10-0.15 mg/kg of morphine intramuscularly at 05:30. At 06:00, a pulse oximeter was attached to the patient and a radial arterial catheter was inserted percutaneously. Two liters of oxygen were administered via nasal prongs and fluid administration was increased to 5ml/kg/hr. Then, 0.5 mcg/kg/min of intravenous GTN (N=16) or placebo (N=14, single blind design) was administered for 10 minutes. Next, anesthesia was induced with 3-5 mg/kg of thiopental and 3-5 mcg/kg of fentanyl, and maintained with 50% nitrous oxide and 0.2 to 1.0% end-tidal isoflurane analyzed by mass spectrometry. Ventilation was controlled and normocapnia maintained. The isoflurane concentration was adjusted to achieve a systolic arterial pressure (SAP) within 20% of the patient's ward SAP. Prior to significant blood loss or clamping of major vessels, the test infusion was repeated for ten minutes during a period of apparently constant surgical stimulation. During this time ventilation and depth of anesthesia were not changed. Arterial blood gases were drawn immediately before and after each test infusion. Linear regression analysis, paired and unpaired t-tests with Bonferroni correction as appropriate were used for statistical analysis. Values cited are mean ± standard error of the mean.

Results. Patients in the placebo and GTN groups were comparable in age, preinfusion hemodynamics, and P_aO_2. Infusion of GTN but not placebo significantly lowered SAP and P_aO_2 both before (SAP 152±7 to 145±7 mm Hg and P_aO_2 100±7 to 94±5 mm Hg) and during anesthesia and surgery (SAP 133±6 to 113±6 and P_aO_2 197±21 to 149±21). However, the changes in SAP did not correlate with the changes in P_aO_2. The changes in C_aO_2 induced by GTN before anesthesia and surgery correlated weakly with those induced during anesthesia and surgery (R=0.68). No significant change occurred in either group in arterial carbon dioxide tension, or the intraoperative arterial-alveolar carbon dioxide gradient (A-a CO_2). Also, the change in C_aO_2 induced by GTN did not correlate with the end-tidal concentration of isoflurane. Finally, the fall in C_aO_2 induced by GTN before anesthesia and surgery (0.25±0.06 ml O_2/dl blood) did not differ from that induced during anesthesia and surgery (0.25±0.07).

Discussion. Our results suggest that controlled ventilation and light levels of inhalational anesthesia do not alter the effects of GTN on pulmonary gas exchange in well hydrated patients. In addition, they suggest that inhibition of hypoxic pulmonary vasoconstriction (HPV) or augmentation of pulmonary alveolar dead space are unlikely explanations for the effects of GTN on P_aO_2. If the former mechanism were responsible, then the fall in C_aO_2 induced by GTN during anesthesia and surgery should have been less than that prior to induction, because inhalational anesthetics partially inhibit HPV. If the latter mechanism were responsible, then the A-a CO_2 should have increased, which it did not. Alternative explanations for GTN's effects on P_aO_2 include reduction in mixed venous oxygenation tension via reduction in cardiac output, or augmentation of intrapulmonary shunting not under control of HPV. We are currently investigating some of these possibilities. Finally, our data indicate no consistent correlation between the change in SAP and C_aO_2 before or during anesthesia and surgery, however, they do suggest that a preinduction trial of 0.5 mcg/kg/min of GTN will demonstrate to the clinician the extent of fall in C_aO_2 to be expected when this same dose of GTN is administered intraoperatively. Supplemental oxygen administration during such trials is recommended.

Title: A COMPARISON OF MIVACURIUM (BW B1090U), SUCCINYLCHOLINE AND ATRACURIUM IN HUMANS DURING NITROUS OXIDE-FENTANYL ANESTHESIA

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Introduction. The new nondepolarizing neuromuscular blocking agent mivacurium chloride* appears to have a duration of action which is shorter than that of currently available nondepolarizing agents, but longer than that of the depolarizing agent succinylcholine.[1,2] Mivacurium has, however, not been compared directly with succinylcholine and a nondepolarizing agent, under the same experimental conditions. We have, therefore, studied the onset, duration and recovery of neuromuscular blockade induced by mivacurium, succinylcholine and atracurium.

Methods. Following approval from our Committee for Human Research 32 patients (ASA physical status 1 or 2) were studied. Premedication was with midazalom 0.02-0.05 $mg \cdot kg^{-1}$ iv. Anesthesia was induced with fentanyl 5-10 $\mu g \cdot kg^{-1}$ iv followed by thiopental 2-6 $mg \cdot kg^{-1}$ iv, whereupon the patient's trachea was intubated without the use of muscle relaxants. Anesthesia was maintained with nitrous oxide 60-70% (end-tidal) and supplements of fentanyl or thiopental. Esophageal temperature was maintained at 35-37 °C and end-tidal CO_2 tension between 30 and 35 mmHg. Supramaximal stimuli of 0.2 msec duration, in a train-of-four (TOF) sequence at 2 Hz, were applied, via subcutaneous needle electrodes, to the ulnar nerve at the wrist. Neuromuscular blockade was assessed by measuring the mechanical evoked response of the adductor pollicis muscle to the first stimulus in each train (T1). When conditions were stable, patients received either mivacurium, 0.2 $mg \cdot kg^{-1}$ (n=9), mivacurium, 0.25, $mg \cdot kg^{-1}$ (n=8), succinylcholine, 1.0 $mg \cdot kg^{-1}$ (n=9) or atracuriium, 0.5 $mg \cdot kg^{-1}$ (n=6) as a rapidly administered iv bolus. Onset, duration, and recovery, were, respectively, the times from injection of drug until the maximum depression of the T1 response, and until T1 returned to 25% and 90% of control. After T1 had recovered to 90% some patients received a second bolus of drug; mivacurium, 0.1 $mg \cdot kg^{-1}$, succinylcholine, 0.5 $mg \cdot kg^{-1}$, or atracurium 0.2 $mg \cdot kg^{-1}$. When T1 then recovered to 5% an infusion was commenced and the rate adjusted to maintain T1 at 5% ± 4% of control. When the infusions were terminated, all patients in the succinylcholine group and 8 in the mivacurium group were allowed to recover spontaneously. The remainder received neostigmine 45 $\mu g \cdot kg^{-1}$ plus atropine, 10-20 $\mu g \cdot kg^{-1}$ iv when T1 had recovered to 10%. The recovery times from T1 = 10% to T1 = 25% and 90% were compared. Statistical comparisons were made by Mann-Whitney U test or Kruskal-Wallis one way analysis of variance, and differences were considered significant at $P < 0.05$.

Results. As expected the onset of neuromuscular blockade was more rapid following succinylcholine than following mivacurium or atracurium (Table 1). The onset with both doses of mivacurium, and atracurium was similar. Duration and recovery were shortest for the succinylcholine group, similar in the two mivacurium dosage groups, and longer in the atracurium group than both mivacurium groups. Following the infusions, recovery from succinylcholine was more rapid than the spontaneous recovery from mivacurium (table 2), with the exception of one patient in whom a phase 2 block developed which could not be antagonised with edrophonium. This patient was not included in the results detailed in table 2. Recovery times following neostigmine were similar for both mivacurium and atracurium and were not different to the times of spontaneous recovery following succinylcholine.

Table 1. Onset, duration and recovery (min) following initial bolus doses of succinylcholine (SUX), mivacurium (MIV), and atracurium (ATRA). All results are mean ± SD.

	Onset*	Duration*†	Recovery*†
SUX (1.0 $mg \cdot kg^{-1}$)	1.0 ± 0.2	8.8 ± 1.7	12.5 ± 2.9
MIV (0.2 $mg \cdot kg^{-1}$)	2.4 ± 0.6	21.9 ± 5.0	32.5 ± 4.8
MIV (0.25 $mg \cdot kg^{-1}$)	2.7 ± 0.8	24.1 ± 3.4	36.5 ± 5.3
ATRA (0.5 $mg \cdot kg^{-1}$)	2.5 ± 0.7	44.9 ± 4.0	65.1 ± 6.6

* $P < 0.05$, succinylcholine compared to mivacurium and atracurium. † $P < 0.05$ mivacurium compared to atracurium.

Table 2. Length of infusions (INFTIME) and recovery times (min) following infusions of succinylcholine (SUX), mivacurium (MIV) and atracurium (ATRA). REC25 and REC90 are the times from T1=10% to T1=25% and 90% respectively. Recovery was either spontaneous (spont) or induced by neostigmine 45 $\mu g \cdot kg^{-1}$ (neo).

	n	INFTIME Range	REC25‡§ Mean ± SD	REC90‡§ Mean ± SD
SUX (spont)	5	19 - 89	1.5 ± 0.3	6.6 ± 2.5
MIV (spont)	8	32 - 186	3.2 ± 1.3	15.5 ± 5.9
MIV (neo)	6	30 - 155	2.0 ± 0.5	10.7 ± 4.6
ATRA (neo)	5	26 - 135	2.6 ± 1.0	9.5 ± 1.8

‡ = $P < 0.05$ SUX (spont) *vs* MIV (spont). § = $P < 0.05$ MIV (spont) *vs* MIV (neo).

Discussion. The time course of neuromuscular blockade following mivacurium had features in common with both succinylcholine and atracurium. Its short duration of action suggests that mivacurium might be considered as an alternative to succinylcholine in situations where the rapid onset of the latter agent is not the principal reason for its use. Mivacurium is metabolized by plasma cholinesterase[1], and it is a theoretical possibility that the administration of the anticholinesterase agent neostigmine might in fact delay recovery. This did not occur in our study. The difference we observed between spontaneous and neostigmine-induced recovery times, following mivacurium infusions was small, and less than has been reported for atracurium.[3] This was perhaps due to a combination of the rapid spontaneous recovery of mivacurium and the relatively slow onset of action of neostigmine.

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Title: A DOUBLE BLIND COMPARISON OF LABETALOL AND NITROPRUSSIDE FOR HYPOTENSIVE ANESTHESIA

Authors: J Cantillo, M.D., ME Goldberg, M.D., S McNulty, D.O., S Sharifi-Azad, M.D., M Torjman, MEd, AT Marr, C.R.N.A., TF Boerner, M.D., S Huffnagle D.O., JL Seltzer, M.D.
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Introduction: Sodium nitroprusside(N) is the medication most commonly utilized to produce deliberate hypotension during general anesthesia. More recently labetalol(L), a combined α and β adrenergic blocking agent, has been advocated for use to induce hypotension in combination with various inhalation anesthetics (1,2). Theoretically, L should avoid several of the possible adverse sequelae associated with the use of N for hypotensive anesthesia such as tachycardia, tachyphylaxis, cyanide toxicity and increased shunt. The purpose of this study was to compare the hypotensive effects of L and N in a double blind fashion during anesthesia for major spine surgery.

Methods: 19 ASA Class I-II patients undergoing major orthopedic spinal procedures gave their informed consent to participate in this IRB approved protocol. Patients were excluded on the basis of a history of MI in the last 6 months, CHF, hypertension, bradycardia (< 55 bpm), heart block > 1°, clinically significant hematologic or hepatic disease and COPD. Monitoring other than those standardly utilized consisted of an arterial catheter, pulmonary artery catheter and electroencephalogram (Lifescan). Anesthetic technique was standardized and consisted of premedication with morphine 0.08 mg/kg and atropine 0.4 mg IM. Induction was with thiopental 4-6 mg/kg and fentanyl 3-5 μg/kg. Endotracheal intubation was facilitated with succinylcholine 1 mg/kg. Maintenance consisted of N_2O 60-70% in O_2 40-30% and isoflurane at an end tidal concentration of up to 0.7%. Muscle relaxation was maintained with vecuronium 0.05 mg/kg. At the surgeons request hypotension was induced in a randomly assigned fashion with either a N infusion (0.02% solution 2 μg/kg/min and increased as needed) or L (10 mg increments every 10 min until goal blood pressure or 300 mg was given) to a mean arterial pressure of 55-60 mmHg. Every patient received an infusion and bolus however only active drug via one route and saline by the other. Systolic, diastolic, mean arterial pressure(MAP), pulmonary artery systolic, diastolic and mean pressure(PAP), pulmonary artery occlusion pressure (PAOP), central venous pressure(CVP) and cardiac output(CO) were measured post induction, pre hypotension, at initial goal hypotension, every 15 minutes thereafter, on request to return to baseline and every 15 minutes until baseline values were achieved. Data was analyzed utilizing multivariate ANOVA with repeated measures. A p value of < 0.05 was considered statistically significant.

Results: Hypotension was easily accomplished with both medications. The time to obtain goal blood pressure took significantly longer with N (55.3 ± 45 min) as opposed to L (21.25 ± 13.4 min) however this was probably secondary to the concentration and dosing of N. The duration of hypotension was also not different between the 2 groups. When the hemodynamic values were compared between the 2 groups no significant difference was seen in CO, MAP, PAOP, SVR, CVP, or stroke volume(SV).

N administration did cause a significant elevation in HR when goal hypotension was achieved as compared to L. The HR also was significantly elevated as compared to baseline pre N administration. This was accompanied by a decrease in SVR as compared to baseline. CO was elevated but did not reach significance until 60 min. L administration did not cause a significant change in CO, HR, PAP or SV when compared to baseline. SVR was significantly decreased when compared to baseline but not different than the N group. There was no significant difference in blood loss or the drop in hemoglobin. The time to obtain normal blood pressure was significantly shorter for N (20.72 ± 20.13 min) then L (43.12 ± 21.70 min).

Discussion: L has been used to induce hypotension in combination with inhalation agents during various surgical procedures (1,2). In this study, administration of L or N allowed easy production of hypotension. In the N group this was the result of a decrease in SVR but at the cost of an increase in HR and CO. In the L group the drop in SVR was not accompanied by change in HR, and CO was maintained at baseline values. This is in contrast to the typical picture of β blocking agents. Fahmy, in an earlier unblinded study demonstrated that L use allowed production of hypotension when compared to N however much larger doses (90-230 mg) were required and duration of effect was 3-6 hours (3). In contrast, our findings agree with those of Scott (4) and Kaufman (5) in that a small dose (29.37 ± 21.94 mg) of L was necessary to achieve goal in our patient population. These results indicate that L allows rapid onset of hypotension (mean of 21 min) that returns to baseline values approximately 43 minutes after the last dose was administered.

In conclusion L is useful in combination with low dose isoflurane to induce hypotension and does not result in the increased heart rate seen with N administration. In addition, prolonged effects from L administration are not seen.

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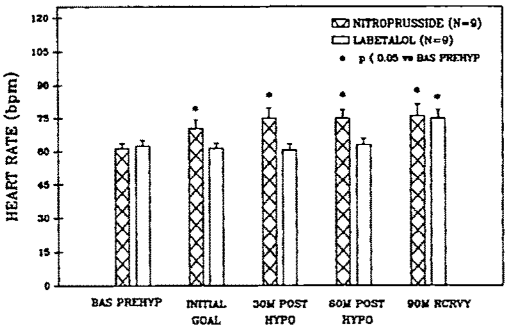
MEAN HEART RATE
AT EACH TIME PERIOD



TITLE: CIRCULATING ENDOTOXINS DURING PEDIATRIC CARDIAC SURGERY
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INTRODUCTION: Endotoxins are known to produce a variety of adverse biological effects, including fever, leukocytosis, complement activation and shock. Endotoxins have been found in the plasma of adults undergoing coronary artery surgery.[1] This study was designed to measure serum endotoxin levels in pediatric patients undergoing cardiac surgery, and to assess their possible role in post-operative pyrexia and morbidity.

METHODS: Twenty pediatric patients undergoing open heart surgery for repair of congenital heart disease were studied following hospital and parental approval. Anesthesia was induced with halothane, N_2O, and O_2, and then maintained with pancuronium, fentanyl (10-50 mcg/kg) and up to 1% isoflurane. Intravenous, central venous and radial artery catheters were inserted after induction of anesthesia. Blood samples for measurement of endotoxin levels were drawn under sterile conditions from a peripheral venous line (control) and collected in sterile pyrogen free tubes. At predetermined times during the surgical procedure and the first 3 post-operative days, additional samples were obtained from the radial arterial line. Samples were also obtained from the arterial blood outlet of the oxygenator of the bypass pump before connection to the patient (control) and at specific times during cardiopulmonary bypass (CPB), from all fluids administered to the patient, and from fluids used to prime the pump. All samples were stored at 4°C for 12-24 hours and then platelet-rich plasma was obtained by centrifuging the blood at 302 r.p.m. for 15 minutes. Plasma then was heat treated for 10 min. to inactivate endotoxin inhibitors. Endotoxins were measured in the samples using Limulus amebocyte lysate (LAL) and a toxinometer ET-201[2] to give quantitative results.[2] Patients had blood cultures done following induction of anesthesia, while on cardiopulmonary bypass, and in the post-operative period if their temperature exceeded 39°C.

RESULTS: All control samples were negative for endotoxins. Endotoxin was detected in a total of 12 patients during the study period. Seven patients had clinically insignificant levels (< 30 pg/ml), two had elevated endotoxins (56-110 pg/ml) at sternotomy, and two at CPB coinciding with similar levels from the oxygenator (25-120 pg/ml). One patient had levels above 30 pg/ml in the immediate post-operative period. All coincided with negative blood cultures. There was no significant difference between those patients who were positive or negative for endotoxin with regards to inotropic support, weight gain, and time to extubation. Low endotoxin levels were found in 2 samples of the ice solution and one sample of Ringer's lactate. All other fluids administered as well as control oxygenator samples were negative for endotoxin. Eleven patients had temperatures of greater than 38.5°C in the post-operative period. Of those, seven required acetaminophen and two patients received cool baths to control temperature. No correlation was found between endotoxin levels and post-operative temperature elevations.

DISCUSSION: Endotoxins are components of gram negative bacteria. In small doses (2 ng/kg), they are potent pyrogens. Larger doses can produce shock.[1] The source of endotoxins in the absence of a demonstable bacteremia must remain a matter of speculation. The two patients who had measurable endotoxin levels intraoperatively did so during CPB in the presence of negative blood cultures. We therefore believe that the endotoxins seen during CPB were derived from "environmental" sources. Endotoxins were found in only 3 of the 160 samples taken from the intravenous fluids and drugs administered to the patients. Similar findings have been reported in adults.[1] Another possible source is increased absorption of endotoxins through the intestinal mucosa damaged by decreased perfusion during CPB. Although we did not find a correlation between post-operative fever or morbidity and the presence of endotoxins, control of endotoxins during cardiac surgery seems desirable. Use of pyrogen free fluids, optimal aseptic precautions during invasive procedures, preoperative decontamination of the intestine and prevention of hypotension during CPB could be effective precautions against the liberation of endotoxins. In summary, we have demonstrated that endotoxins were found in the plasma of pediatric patients undergoing cardiac surgery. Relationship to post-operative temperature elevation could not be demonstrated.

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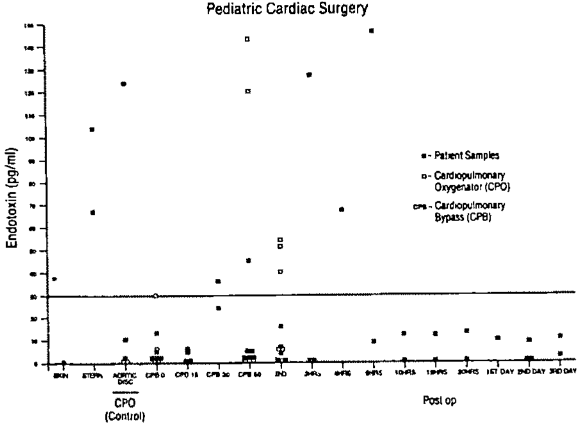

Title: **Analgesic Effect of Continuous Intercostal Nerve Block Following Thoracotomy**

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Introduction. Conventional intercostal nerve block adequately relieves pain following thoracotomy.[1,2] However, prolonged analgesia would require repeated local anesthetic injections. This study aims to determine: (1) the efficacy of continuous intercostal nerve block (ICNB) for post-thoracotomy pain relief, (2) the effect of continuous ICNB on post-operative lung function, and (3) the extent of systemic bupivacaine absorption.

Methods. Twenty ASA II and III patients (14 men, 6 women, 51-91 kg, 44-81 years of age) consented to be randomly assigned to either the bupivacaine group or placebo group in this double blind study, as approved by the Human Research Committee. Thoracotomies were performed under general anesthesia for lobectomy (13), bullectomy (2) and trans-thoracic oesophageal surgery (5). All incisions were made in the posterior 5th intercostal space. Intraoperative fentanyl doses were limited to 2 ug/kg at the time of skin incision and then 1 ug/kg/h as needed. Before wound closure and under direct vision, the surgeon inserted 2 epidural catheters subpleurally, 3-4 cm into the posterior intercostal spaces; one catheter above and one below the incision site. Each catheter was then sutured in place and its other end was brought out near the incision site.

In the bupivacaine group (10), 10 ml of 0.5% bupivacaine with 1/200,000 epinephrine was injected through each of the 2 catheters over 5 min after a negative aspiration test. The placebo group (10) received 10 ml of saline through each catheter. All patients were awake and monitored in ICU during injections. Subsequent top up doses, using the same dose and solution, were given to each group every 6 h for 24 h. In the case of inadequate analgesia, patients received repeat doses of morphine, 0.06 mg/kg i.v. upon request.

Visual analog pain score was assessed 10 min before and 1 h after each injection. Pulmonary functions (FEV1, FVC and PEFR) were assessed 1 h before and 1 h after each injection.

Arterial blood samples were obtained at 0, 2.5, 5, 10, 20 and 60 min after each injection. All blood samples were immediately centrifuged and the plasma was frozen at -20° C. Bupivacaine concentration was determined by gas chromatography. Statistical analyses were performed using Chi-square and paired t-test.

Results. Visual analog pain score dropped significantly following 2nd, 3rd and 4th intercostal bupivacaine injections (Table 1). Similarly, mean postoperative morphine requirement in 24 h was much lower in the bupivacaine group (16.6 ± 4.6 mg, vs 35.8 ± 7.2 mg, $p<0.04$). No difference in age, sex, height, weight or the mean dose of fentanyl given intraoperatively was noted in either group.

FEV1, FVC and PEFR fell to 25%, 30% and 15% respectively of preop value in both groups and failed to rise in spite of intercostal bupivacaine injections. Peak serum bupivacaine concentrations (ug/ml) achieved 10-20 min after each subsequent injection were 0.50 ± 0.13, 0.57 ± 0.1, 0.81 ± 0.13 and 1.19 ± 0.18 (see fig.).

Discussion. This simple technique of continuous intercostal nerve block controlled post-thoracotomy pain effectively. However, it did not improve postoperative lung function. Systemic bupivacaine accumulation was seen after repeated intercostal injections, with the peak levels below toxic range, i.e. <4 ug/ml.

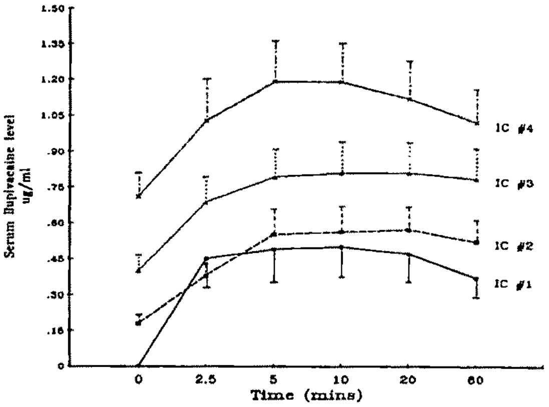
Table 1

Visual Analog Pain Score following IC Injections

	Bupivacaine group N = 10		Placebo group N = 10	
	pre	post	pre	post
No. 1	--	7.0 ± 0.8	--	8.1 ± 0.6
No. 2	5.1 ± 1.1	2.5 ± 0.8 p<0.02	6.2 ± 0.7	4.6 ± 1.0 p<0.03
No. 3	4.2 ± 1.0	1.5 ± 0.8 p<0.009	4.2 ± 0.9	3.8 ± 1.0 N.S.
No. 4	5.5 ± 1.1	1.5 ± 0.8 p<0.006	4.4 ± 0.8	3.2 ± 0.8 N.S.

Values are means ± SE; N.S.= nonsignificant

SYSTEMIC BUPIVACAINE ABSORPTION



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Title: COMPUTER SIMULATION DEMONSTRATING MECHANISM OF INHIBITION OF HYPOXIC PULMONARY VASOCONSTRICTION (HPV) BY ALMITRINE BISMESYLATE

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INTRODUCTION: Almitrine bismesylate has been reported to improve P_{aO2} and decrease P_{aCO2} in patients with chronic obstructive pulmonary disease (COPD) (1). Its effects on HPV are controversial and no effect (2), inhibition (3), and enhancement (4) of HPV have all been reported. A computer simulation of the pulmonary circulation based on detailed morphologic and biodynamic characteristics of the lung (5,6) allows predictions of blood flow distribution and pulmonary artery pressure (PAP) for comparison with experimental measurements when the condition for 2 compartments (e.g. a hypoxic lobe or lung versus the rest of the lung) are known. The mechanisms by which variables such as mixed venous $P_{\bar{v}O2}$, which stimulates, and cardiac output (CO), which modifies, the HPV response can then be quantitatively evaluated.

METHODS: In the computer simulation for almitrine, the data for PAP, CO, left atrial pressure (LAP), P_{aO2} and $P_{\bar{v}O2}$, and alveolar end-expiratory pressures (P_{alv}) were measured. The pleural pressure (P_{pl}) was estimated at -2.0 cmH$_2$O since the chest was closed. These conditions determine the vascular tone and the program then calculates sequentially the diameter and pressure drop across all 22 orders of arteries and veins and of the capillary sheet to arrive iteratively at the unique blood flow distribution at which the resulting pulmonary artery pressures are equal for both regions. The amount of constriction is calculated as the ratio of the diameter of the vessel constricted to the diameter relaxed when the transmural pressure is zero. A constriction ratio of 0.6 corresponds to a maximal hypoxic constriction and a value of 1.0 to no constriction.

RESULTS: The figure shows the computer simulation for the relative blood flow and the pulmonary artery pressure changes observed in dogs subjected to left lung hypoxia when high-dose almitrine (14.3 µg/kg/min) was infused (3). When both lungs receive 100% O_2-no drug (star), the relative blood flows for the right lung ($R\dot{Q}_R$) and the left lung ($R\dot{Q}_L$) are 1.0. When the left lung receives hypoxia-no drug (circles), the left lung vasoconstricts and the blood flow is diverted to the right lung. This vasoconstriction for the left lung is represented by the constriction ratio change from 1.0 to 0.70; the blood flow diversion is represented by the $R\dot{Q}_L$ decrease from 1.0 to 0.65. At the same time, the 100% O_2 ventilated right lung does not experience any vasoconstriction so that the constriction ratio remains at 1.0; since the hyperoxic lung accommodates the blood diverted to it, the $R\dot{Q}_R$ increases from 1.0 to 1.29. With the addition of almitrine (triangles), the increase in left lung vasoconstriction is represented by the constriction ratio decrease from 0.70 to 0.65 and the decrease in blood flow diversion is represented by the $R\dot{Q}_L$ increase from 0.65 to 0.91. However, high-dose almitrine also causes vasoconstriction of the 100% O_2 ventilated right lung as represented by the constriction ratio decrease from 1.0 to 0.69; this diversion of blood back into the hypoxic lung is represented by the $R\dot{Q}_R$ decrease from 1.29 to 1.07.

DISCUSSION: The computer simulation provides an explanation for experimental data. High-dose almitrine bismesylate caused vasoconstriction of the hyperoxic right lung thereby diverting blood back to the hypoxic left lung. Interestingly, other pulmonary vasoconstrictors such as high-dose dopamine appear to reduce the effectiveness of HPV in a similar manner (7).

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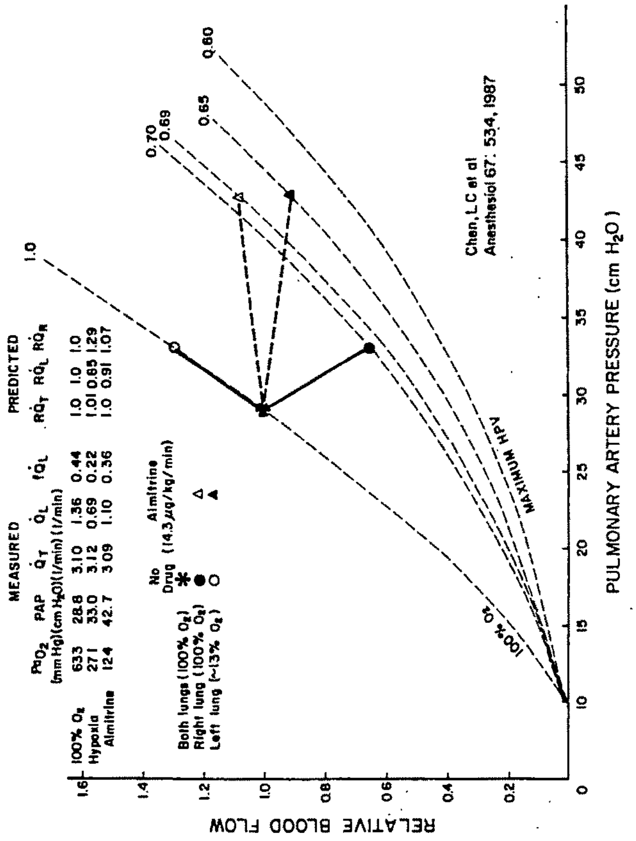

Title: Hemodynamic and Postoperative Ventilatory Effects of Sufentanil Supplementing General Anaesthesia

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Introduction. Despite a few case reports of respiratory arrest (1,2), no detailed analysis of postoperative respiratory depressive function by sufentanil has been investigated. Having shown that the optimal time to blunt the cardiovascular response by intravenous lidocaine is 3 minutes prior to endotracheal intubation (3), we compared the effect of 1.0 mcg kg^{-1} sufentanil (S) with that of low-dose 0.5 mcg kg^{-1} plus lidocaine 1.5 mg kg^{-1} (LS) on cardiovascular response to tracheal intubation and postoperative respiratory depression by respiratory inductive plethysmography in a double-blinded controlled study.

Methods. Human Experimentation Committee approval and informed consent were obtained. Thirty healthy patients, aged between 18-60, undergoing elective surgical procedures that required tracheal intubation were studied. No preoperative sedation was given. Baseline flow-volume spirometric measurement and respiratory inductive plethysmographic calibration were done preoperatively. Patients were randomly allocated into 3 groups: control (C), lidocaine with sufentanil (LS) and sufentanil (S). All patients were primed with 0.5 liter crystalloid pre-induction. Baseline data were collected at five minutes post-oxygenation. After precurarization, at Time -3 min, either normal saline or lidocaine 1.5 mg kg^{-1} was injected, followed by normal saline or sufentanil (0.5 or 1.0 mcg kg^{-1}). At Time -1 min, thiopentone was titrated until loss of consciousness, and followed with succinylcholine 1.5 mg kg^{-1} for endotracheal intubation. Controlled ventilation with 70 percent nitrous oxide and 30 percent oxygen was initiated. No stimulation to patient was allowed for the subsequent five minutes for hemodynamic measurements. Anaesthesia was supplemented with vecuronium and isoflurane if necessary to maintain hemodynamic parameter within 20% of preoperative level. Ventilation was controlled to end-tidal CO2 of 35-40 mmHg. No further narcotic was given intra-operatively. At end of operation, patients were all extubated with zero expiratory concentration of isoflurane. Postoperatively, pulmonary functions were monitored by the respiratory inductive plethysmograph for one hour. Data were expressed in mean ± SEM. Statistical analysis was done by a one-way ANOVA and was followed by multiple range test during post-hoc analysis of significant overall F's.

Results. There were no differences among the three groups in age, weight or duration of surgery. Groups LS and S reduced the thiopental requirements by 28% and 40% respectively. Both treatment groups significantly suppressed the hemodynamic responses to intubation. Postoperatively, PaCO2 level was significantly elevated in group S at 30 minutes (Table 1). Dose-related respiratory depression patterns were observed. Incidence of patients with apnea, rate of apnea index (Figure 1), and duration of apnea were higher in LS and S groups, particularly over the initial 10-20 minutes post-operation. Group S also showed significantly slower respiratory frequency and prolonged expiratory time. No differences were observed in inspiratory time, tidal volume, minute ventilation, respiratory drive, % rib and % abdominal ventilation.

Table 1

	C (n=10)	LS (n=10)	S (n=10)
Age (yr)	33 ± 4	38 ± 3	27 ± 2
Wt (kg)	73.3 ± 5.0	70.1 ± 3.3	70.6 ± 3.5
Surgery (min)	70.8 ± 8.2	74.9 ± 10.7	67.1 ± 8.8
thiopental (mg kg^{-1})	5.0 ± 0.2	3.6 ± 0.2 *	3.0 ± 0.2 * +
PaCO2 (mmHg)	40.4 ± 1.7	45.5 ± 2.0	50.0 ± 3.1 **
HR (bpm) (Baseline)	64 ± 4	72 ± 5	69 ± 2
HR (bpm) (1 min post-intubation)	93 ± 5	75 ± 3 *	74 ± 4 *
SBP (mmHg) (Baseline)	123 ± 8	131 ± 8	133 ± 5
SBP (mmHg) (1 min post-intubation)	165 ± 8	115 ± 6 *	107 ± 3 *

mean ± SEM
* $p<0.005$ vs C ** $p<0.01$ vs C + $p<0.05$ vs LS

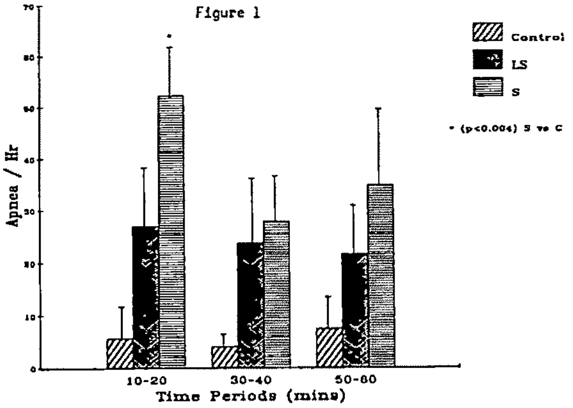

Figure 1

Discussion. Our findings indicate that, when the recommended induction dose of sufentanil (1 mcg kg^{-1}) was used in balanced anesthesia during short surgical procedures, the risk of postoperative respiratory depression overrides its advantages in attenuating the pressor responses to intubation. The use of low dose sufentanil (0.5 mcg kg^{-1}) with lidocaine (1.5 mg kg^{-1}) achieves comparable attenuation of hemodynamic responses to intubation, but less respiratory depression.

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Title: CARDIOVASCULAR EFFECTS OF MIVACURIUM CHLORIDE (BW B1090U) DURING HALOTHANE, ISOFLURANE, OR NARCOTIC ANESTHESIA

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Introduction. Mivacurium is a new nondepolarizing neuromuscular blocking agent with a short duration of action currently undergoing clinical trials to evaluate its neuromuscular and cardiovascular effects.[1-4] Effects of mivacurium during nitrous oxide-halothane anesthesia have not been reported. The purpose of this study is to further evaluate the cardiovascular responses that occur following the administration of mivacurium to surgical patients during halothane, isoflurane or nitrous narcotic anesthesia.

Methods. One hundred twenty-six patients of either sex, ASA I-II, aged 18-70 years, weighing less than 110 kg were studied after institutionally approved informed consent was obtained. Patients were premedicated with morphine (0.10-0.15 mg/kg) and atropine (0.004-0.008 mg/kg) 45-60 minutes prior to induction of anesthesia. Anesthesia was induced with thiopental 4-8 mg/kg and maintained with nitrous oxide (60-70%), oxygen (30-40%) and halothane (n=27) or isoflurane (n=27) (end-tidal concentration adjusted to yield a total MAC of approximately 1.25). In a third group (n=72), anesthesia was maintained with nitrous oxide (70%) in oxygen and fentanyl (1-2 μg/kg), supplemented with additional thiopental and fentanyl as clinically indicated. Ventilation was controlled to maintain end-tidal CO_2 between 35-40 mmHg (Perkin-Elmer mass spectrometer). Temperature was maintained in the normal range. Twitch response of the adductor pollicis muscle to ulnar nerve stimulation was elicited by supramaximal square wave pulses of 0.2 msec duration at a frequency of 0.15 Hz quantitated using an FT10 transducer. After stabilization of the twitch response and cardiovascular base line, one of six doses of mivacurium (0.03, 0.05, 0.10, 0.15, 0.20, 0.25 mg/kg) were administered as a rapid bolus (over 2-3 seconds). In two additional groups of patients, cardiovascular measurements were made after slower injection (30 sec) of the two highest doses of mivacurium. The EKG and pulse (HR) were monitored continuously throughout the study. Systolic, diastolic and mean arterial pressure (MAP) were monitored every minute for ten minutes, using an automated oscillotonometer in the lower dose group (0.03-0.05 mg/kg) and transduced arterial pressure via indwelling radial artery catheter in those patients receiving drug doses estimated to be ED95 or greater. Data are expressed as mean ± SEM and were analyzed using ANOVA or students "t" test as appropriate, with $P < 0.05$ being considered significant.

Results. MAP and heart rate as % of control at 1, 2 and 5 minutes following bolus administration of mivacurium during halothane, isoflurane or nitrous narcotic anesthesia are presented in Table 1. Analysis of data indicate that at doses up to and including 0.15 mg/kg (approx. 2 x ED95) there were no significant changes in MAP. Changes in MAP were less than 10 percent up to and including 0.15 mg/kg during all three anesthetic techniques. At 0.20 mg/kg and 0.25 mg/kg (2.5 and 3 x ED95), rapid administration of mivacurium resulted in a significant fall in MAP at one and two minutes. These changes were of short duration and within five minutes the MAP was within 10% of control in 24/27 patients in this group. With slow injection (over 30 sec) of large bolus doses (0.20-0.25mg/kg) there was no significant change in MAP. (Table 2) There was no significant change in heart rate at any time.

Discussion. Bolus administration of mivacurium in doses up to and including 0.15 mg/kg (ED95 x 2) had no significant effect on mean arterial pressure or heart rate following drug injection during halothane, isoflurane or narcotic anesthesia. Rapid administration of mivacurium, exceeding 2.5 x ED95, resulted in brief decrease in mean arterial pressure. When the same large doses of mivacurium were administered slowly (over 30 sec) there were no changes in mean arterial pressure. Cardiovascular effects following rapid administration of large doses of mivacurium may be attributed to a relatively weak histamine releasing property of mivacurium.[2]

Table 1.

Anesth	Dose	MAP (% Cntrl)			HR (% Cntrl)		
Group	(mg/kg)	1	2	5	1	2	5 min
Narc	0.15	92	96	97	103	98	93
Hal	0.15	98	98	95	101	98	94
Iso	0.10	99	99	101	97	96	95

Table 2.

Anesth	Dose	MAP (% Cntrl)			HR (% Cntrl)		
Group	(mg/kg)	1	2	5	1	2	5 min
Narc	0.20	80*	83*	90	107	103	99
(rapid)	0.25	82*	73*	89	107	113	99
Narc	0.20	97	96	95	98	95	89
(slow)	0.25	95	95	104	102	97	95

* $P < 0.05$ vs control value
SEs omitted for space

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Title: FIBEROPTIC EVALUATION OF ENDOBRONCHIAL TUBE POSITION: RED RUBBER VS POLYVINYLCHLORIDE

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Introduction. Smith et al have recently suggested that clinical observations were unreliable in the assessment of polyvinylchloride (PVC) endobronchial tube placement.[1] They noted that in 48% of their patients, fiberoptic bronchoscopy (FB) revealed malpositions of the tube, while clinical criteria had suggested that the endobronchial tube was satisfactorily placed. Red rubber (RR) endobronchial tubes are still widely used and are often claimed to provide more stable and reliable lung separation. The aim of the current study was to assess whether clinical signs allowed more accurate confirmation of adequate positioning with RR tubes than with PVC tubes.

Methods. After written informed consent had been obtained, 20 adult patients (pts), scheduled for thoracic surgery, were randomly assigned to a PVC or RR group. Following inducton of anesthesia, 10 pts in the PVC group were intubated with appropriately-sized left-sided disposable PVC endobronchial tubes (Bronchocath, NCC) while in the 10 pts of the RR group left-sided nondisposable Robertshaw tubes were placed. The anesthesiologists assigned to the cases determined the correct placement of the tubes and satisfactory lung separation by standard clinical criteria. The position of the tubes was adjusted until clinically satisfactory lung separation had been achieved. A single investigator performed all FB and assessed adequacy of tube placement according to the criteria listed in Table 1. Clinical and FB assessments were performed in the supine (SUP) and lateral (LAT) positions. The anesthesiologist responsible for the clinical evaluation were "blinded" to the bronchoscopic findings. The statistical significance of the association between the incidence of malpositions detected by FB and the use of RR or PVC was assessed by chi-square analysis.

Results: The demographics and distributions of right and left-sided thoracotomies were similar for both groups. Lung separation was satisfactory in both groups. In the supine position, 11 malpositions were detected by FB in 8 pts (40%), while in the lateral position only 4 FB malpositions were noted in 4 pts (20%) (Table 1). No statistically significant differences in the incidence of malpositions were observed between the RR and PVC groups. The comparison of the mean values of PaO_2, tidal volume(TV) peak airway pressure, (PAP) and $PaCO_2$ during two lung ventilation and one lung ventilation(OLV) between both types of tubes were not significant (Table 2). Compared to the correct position (Fig 1), in most undetected malpositions the tube was placed too far into the left main bronchus beyond the bronchial carina (Fig 2). In only two cases the tube was not appropriately advanced and fiberoptic bronchoscopy revealed more than half of the bronchial cuff partially obstructing the right main bronchus orifice (Fig 3).

Discussion. Our findings confirm that the incidence of malpositions, revealed by FB, is similar for both types of tube. The fact that a large number of malpositions, which were missed by clinical evaluation, were revealed by bronchoscopy adds weight to the recommendations of Smith et al.[1] Although RR tubes differ from PVC tubes in shape and cuff-location, the correct placement of either of these tubes will often require fiberoptic confirmation. Since no differences in incidence of malpositioning, PaO_2, $PaCO_2$, and PAP were found between RR and PVC, both types of tubes can be equally used to adequately manage OLV. Choice will depend upon personal experience, infection control, and cost-effectiveness.

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Table 1: Incidence of Malpositions

Type of Tube	RR(10pts)		PVC(10pts)	
Patient Position	SUP	LAT	SUP	LAT
Bronchoscopy via tracheal lumen				
1. Carina not visualized	2	0	3	0
2. Right main brochus not visualized	1	0	0	0
3. More than half of the bronchial cuff visualized	0	1	0	1
Bronchoscopy via bronchial lumen				
1. Tracheal carina visualized	0	0	0	0
2. Left upper bronchus not visualized	3	1	2	1

Table 2: Oxygenation

	RR		PVC	
	2-Lung	OLV	2-Lung	OLV
PaO_2 mmHg	484 ± 78	192 ± 128	436 ± 116	191 ± 94
TV ml	657 ± 116	634 ± 164	656 ± 132	644 ± 118
PAP cmH_2O	22 ± 4	30 ± 5	18 ± 2	28 ± 3
$PaCO_2$ mmHg	34 ± 8	38 ± 7	32 ± 3	36 ± 4

Mean ± SD (Student t-test)

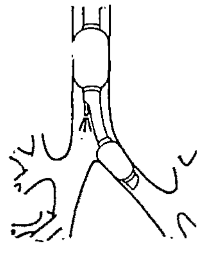

Figure 1

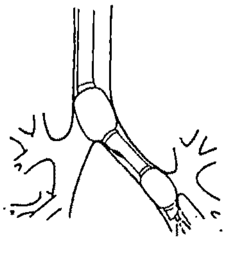

Figure 2

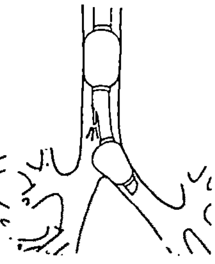

Figure 3

TITLE: MORE FREQUENT PERFORATION BY PULMONARY ARTERY CATHETERS DURING HYPOTHERMIA

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Introduction. Pulmonary artery (PA) pressure monitoring has become increasingly popular since its introduction in the early 1970s. Complications such as dysrhythmia are common (72% of patients [1]), but relatively benign. PA perforation occurs in 0.06% [2] to 2.00% of all patients, regardless of clinical context, however, 37% of these perforations occur in patients undergoing cardiac surgery [1], of which over half lead to fatal outcomes [3]. The risk of PA rupture increases with age, anticoagulation, PA hypertension and hypothermia [4]. This last factor is a constant hazard accompanying all cardiac surgeries performed during hypothermic conditions. This study was undertaken in an in-vitro model to determine if the relative perforating potential of a PA catheter is related to ambient temperature.

Methods. A water-filled, temperature-controlled testing chamber, separated into a larger and smaller subchamber by a 12.7-micron polyethylene membrane, was used (Fig.). The catheter to be tested was fixed 15 cm from its tip in a 1-cm ID support tube with 1 cm of its distal tip extending out of the support tube. It was approximated (1.5 mm) at a 90° incident angle to the membrane. The membrane was then made to pulsate 5- to 6-mm into the larger subchamber at a rate of 80 pulsations/min by means of a hydraulic piston. A strain gauge, mounted in the smaller subchamber, was used to measure the number of pulsations to perforate the membrane, as demonstrated by a decrease in pressure in the smaller subchamber. Five 7.0-Fr Edwards PA catheters, recovered after use in patients, were tested 5 times each at 35, 30 and $25^{\circ}C$ without moving the catheter between tests. A new membrane was inserted between each test. Significant differences ($P < 0.01$) and insignificant differences ($P > 0.10$) were determined by ANOVA.

Results. Time to perforation was significantly shorter as temperature was decreased (Table). There were no significant differences between catheters or between tests at the same temperature.

Discussion. PA catheters often migrate distally during open-heart operations [1], sometimes as much as 5 cm, and come to lie in lobar or segmental branches of the PA. The perforating potential of these catheters has been shown to increase markedly as the angle of incidence increases above 50°. At 90°, this perforating potential is maximal and well suited for a worst-case evaluation, and this is the angle at which previous in-vitro studies have been performed [5]. Because the Swan-Ganz PA catheter tip tends to curve or may abut a vessel bifurcation, it may assume an acute angle in-vivo, as well. This in-vitro study objectively demonstrated a 500% reduction in perforation time as the temperature was lowered from 35 to $25^{\circ}C$. One would also expect the in-vivo perforation potential to increase dramatically and be exacerbated by distal migration. Although hypothermia can not be eliminated from many open-heart procedures, this study supports withdrawing the catheter 5 cm, so that it lies in the main PA before the onset of hypothermia, to reduce the risk of PA perforation.

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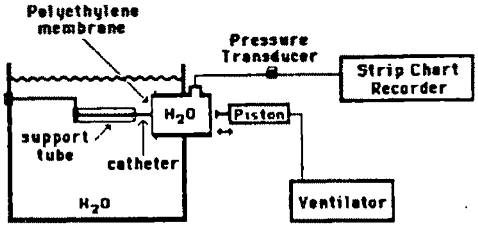

Figure: The catheter test chamber used to determine catheter perforating potential.

Table. Effect of Temperature on the Perforation Potential of PA Catheters

	Temperature of Water Bath ($^{\circ}C$)		
	35	30	25
Number of pulses to perforation			
Mean	488*	309*	97*
± SD	280	242	234
Range	174-1427	5-809	5-472

*$P < 0.01$ when compared with other mean values.

Title:
CONTINUOUS IN VIVO ASSAY OF HEPATIC LIPOPEROXIDATION IN THE RAT: HALOTHANE AND CHLOROFORM COMPARED

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Introduction. The spontaneous emission of extremely low intensity light (chemiluminescence) by organs not possessing a luciferin/luciferase system was described in 1961 (1). It has been suggested that changes in organ chemiluminescence might be used as a continuous non-destructive assay of lipoperoxidation (2). This potentially injurious process can result from oxidation or reduction by one of several species of oxygen free radicals (3). The biochemistry of low-level chemiluminescence (4) and the possibility that oxygen-derived free radicals might play a role in tissue injury (5) have been the subject of recent reviews.

Brown used an in vitro assay technique to demonstrate that chloroform's hepatotoxicity in the rat is associated with hepatic microsomal lipoperoxidation, the onset of which occurs 30 minutes following its administration (6). In my laboratory, continuous in vivo measurements of hepatic chemiluminescence have provided parallel findings (7). In the same study, inhalation of isoflurane, an anesthetic subject to minimal biodegradation was not associated with increased chemiluminescence. In vitro measurements by Brown et al have shown the effect of halothane on hepatic lipoperoxidation to be quantitatively different from that of chloroform; diene conjugates increased but glutathione stores remained intact (8). Hepatocellular necrosis observed in rats anesthetized with chloroform was not seen in phenobarbital-induced animals administered halothane (8). Since in vitro measurements provide only single observations after sacrifice of the animal, and since observation of chemiluminescence can offer a continuous in vivo assay, the following study was performed.

Methods. This investigation was approved by our Institutional Animal Care and Use Committee. Six male phenobarbital-induced Wistar rats weighing 180-200 g were studied as previously described (7). Chemiluminescence of the exposed liver was measured continuously using a single-photon-counting apparatus (2). After anesthesia was induced with intraperitoneal phenobarbital (75 mg/kg), a 30 minute period of oxygen breathing verified stability of the preparation. Following this, administration of 1.3% halothane in oxygen was begun and continued for two hours while hepatic chemiluminescence was continuously observed.

Results. Comparison of the effects of halothane and chloroform on hepatic chemiluminescence in the phenobarbital-induced rat is shown in the table. Hepatic light output was identical in the control periods which preceded administration of either chloroform or halothane ($p > 0.5$); during these 30 minutes, hepatic light output remained constant. Chemiluminescence began to increase 30 minutes after administration of halothane, twice as long as that following an equipotent dose of chloroform ($p < 0.002$). Peak levels were not attained until over an hour after administration of halothane, more than than twice that which had been observed with chloroform ($p < 0.001$). The increase in light emission accompanying halothane was only one-third that which had been observed with exposure to chloroform ($p < 0.002$). Light emission remained constant during the remaining period of observation.

Discussion. While increased chemiluminescence accompanies administration of halothane to the phenobarbital-induced rat, the times to onset and to peak light emission were significantly longer than those previously observed when chloroform had been administered (7). The absolute increase in chemiluminescence produced by halothane was also considerably less than that accompanying chloroform administration. It is likely that this is a consequence of the differential effects of halothane and chloroform on glutathione stores originally described by Brown et al (8), a phenomenon which significantly influences the in vivo effects of these two agents on hepatic lipoperoxidation.

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EFFECT OF CHLOROFORM AND HALOTHANE ON RAT LIVER CHEMILUMINESCENCE

	CHLOROFORM		HALOTHANE	
	Time (sec)	Counts/Sec	Time	Counts/Sec
Control	0	832 ± 94	0	894 ± 59
Onset	15.5 ± 2.1^{+}	N/A	30.2 ± 2.7^{+}	N/A
Peak	26.7 ± 3.4^{++}	1887 ± 139^{+++}	62.8 ± 4.3^{++}	1239 ± 127^{+++}

Means ± SEM
N = 6 for each anesthetic

Chloroform and halothane differ significantly
$^{+}$time to onset of increased chemiluminescence, $p < 0.002$
$^{++}$time to maximum increase in chemiluminescence, $p < 0.001$
$^{+++}$magnitude of maximum increase in chemiluminescence, $p < 0.002$

Title: THE NON-LINEAR ANESTHETIC POTENCY OF NITROUS OXIDE AT SUB-MAC LEVELS IN THE RAT

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Introduction: When nitrous oxide (N2O) is used in combination with a volatile anesthetic, the clinical concensus is that the requirement of the volatile anesthetic linearly decreases as the N2O concentration is increased. However, previous evaluations have failed to provide a clear and consistent linear definition in the dose-response interaction of N2O and volatile anesthetics.(1,2) In the present study, we evaluated whether N2O (in combination with enflurane [E], isoflurane [I], or halothane [H]) made a linear contribution to MAC.

Methods: With prior approval by the Animal Studies Subcommittee, male, Sprague-Dawley rats ($n = 27$) of similar ages and weights were separated into three equal groups. Each rat was randomized to receive either E, I, or H throughout the study period; and received three N2O concentrations (0, 15, and 75%) in systematic variation. Following induction and tracheal intubation a 90 minute anesthetic stabilization period was begun for the initial N2O concentration (with a 60 minute anesthetic stabilization period allowed for each subsequent N2O change). Anesthetic equilibrium was verified by mass spectrometry sampling of end-tidal gases. MAC was determined at each N2O concentration with a standard tail clamp method.(3) Physiological parameters (pH, PaO2, PaCO2, mean arterial pressure, hematocrit, and temperature) were maintained within normal limits. The physiological data were tested for differences within a volatile anesthetic group (between the different N2O concentrations) by analysis of variance. The additive MAC levels for each volatile anesthetic group were graphically represented by plotting the end-tidal N2O concentration (0, 15, or 75%) versus the end-tidal concentration of the volatile anesthetic necessary to achieve 1.0 MAC. An additive MAC line for each volatile anesthetic was drawn through the 0% and 15% N2O points and extrapolated to the 75% N2O concentration. The predicted requirement of the volatile anesthetic at 75% N2O (based upon the change in volatile anesthetic between 0 and 15% N2O) was then compared with the observed volatile anesthetic requirement at 75% N2O by performing a mean t-test. $P<0.05$ was considered significant.

Results: There were no significant differences in the physiological data. The volatile anesthetic requirement decreased as the N2O concentration increased. However, it did not do so linearly. The observed volatile anesthetic requirement at 75% N2O was always significantly greater than that predicted by the 0-15% N2O additive MAC line. This indicates that N2O was a more efficient anesthetic on a unit basis when concentrations between 0-15% were utilized as compared to concentrations greater than 15% (see figure 1).

Discussion: In previous studies N2O has not produced a clear and consistent definition of linearity in its dose-response relationship with a volatile anesthetic.(1,2) This may be due to methodological differences, specific properties of a volatile anesthetic's interaction with N2O, or other neurodynamic properties.(3) The present study was designed to evaluate whether the possible non-linear summation of N2O and a volatile anesthetic is due to unique properties of a particular anesthetic, or a general property of volatile anesthetics. In addition, N2O was evaluated at opposite ends of its clinical spectrum to determine maximal differences in potency. In the present study N2O was found to summate in a non-linear fashion with all three volatile anesthetics, and indicates that the observed non-linearity of N2O may be common to all volatile anesthetics. In practical terms, the ability of N2O to reduce the requirement of a volatile anesthetic necessary to achieve MAC was more than twice as efficient at N2O concentrations less than 15% as compared to concentrations greater than 15%. We conclude that in the rat, the effect of N2O (potency) upon the requirement of a volatile anesthetic agent may be non-linear. This non-linearity may be pertinent when deciding upon a N2O concentration in the clinical setting, and merits further evaluation. If the concept is verified the anesthesiologist may choose a lower concentration of N2O that maximizes anesthetic potency and minimize undesirable side effects

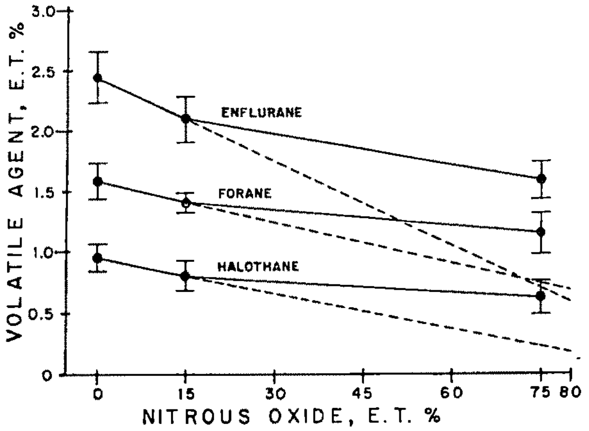

Figure 1 - percent end-tidal (E.T.) volatile agent required to obtain a 1.0 MAC level of anesthesia in the presence of three different concentrationsof N2O (0, 15, and 75%). The dashed line representsa predicted N2O anesthetic contribution based upon the volatile agent requirement change between 0 and 15%. The predicted N20 value at 75% was compared with the observed value by a mean t-test. All three volatile anesthetics had a greater volatile agent requirement at 75% N2O than that predicted ($P<0.05$).

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Title: A NEW LOCAL ANESTHETIC - ROPIVACAINE - ITS EPIDURAL EFFECTS IN MAN

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Introduction. Ropivacaine is a new amino amide local anesthetic agent which is similar in structure to mepivacaine and bupivacaine (1). Pharmacological studies in isolated nerves (1) and intact animals have indicated that ropivacaine possesses an anesthetic profile similar to that of bupivacaine (2). Moreover, this agent has been reported to be less cardiotoxic than bupivacaine (3). Based on the results of these animal studies, it appeared warranted to conduct human studies to determine the clinical effects of ropivacaine.

Methods. The current study evaluated the anesthetic properties of 0.5, 0.75 and 1% ropivacaine in orthopedic patients in whom lower limb surgical procedures were performed. The study was approved by the human research committee at our institution and informed written consent was obtained from all participants in the study. Fifteen patients varying in age from 30-42 years participated in this study. The subjects consisted of 12 males and 3 females. Control blood pressure, heart rate, EKG were taken prior to performance of the epidural block. Epidural blockade was performed with patients in the lateral decubitus position. An 18 gauge Tuohy needle was inserted into the epidural space at the L3-4 level using a loss of resistance technique. Following identification of the epidural space 3ml of 0.5%, 0.75% or 1.0%, ropivacaine were injected into the epidural space. Three minutes after the initial test dose, 17ml of ropivacaine in the designated concentration were then administered through the needle. A total of 20ml of 0.5% (100mg), 0.75% (150mg) or 1% (200mg) were administered. Five patients were studied at each concentration. Sensory anesthesia was evaluated at 2 min. intervals by means of a pin prick for the first 30 min. following injection of the drug. Thereafter, sensory anesthesia was evaluated at 15 min. intervals until complete regression occurred. Motor blockade, was evaluated at the same time intervals on a 0-3+ scale using the Bromage scale. Heart rate, EKG, B.P. were recorded at 2 minute intervals for the first 30 minutes and at 5 minute intervals thereafter. Venous blood samples were drawn from an antecubital vein prior to and at 2, 5, 10, 15, 30, 60, 120, 180, 240 minutes after the epidural administration of ropivacaine. Whole blood ropivacaine concentrations were determined by a gas-chromatographic technique. Data were analyzed by one way analysis of variance (ANOVA). A p value of 0.05 or less was considered significant. Results are expressed as mean ± standard deviation.

Results. Onset of sensory anesthesia to the T12 dermatomal level occurred within 6 minutes with each concentration. (Table 1) The maximum level of sensory anesthesia increased in a concentration dependant fashion. Duration of sensory anesthesia at the T12 dermatomal level increased from 255 ± 33 minutes with the 0.5% solution to 356 ± 34 minutes with the 1% concentration ($p < 0.05$). Minimum motor block was present when the 0.5% solution was employed. An average 2+ motor block was achieved with the 0.75% and 1% concentrations. (Table 1) Minimal changes in blood pressure were observed with any of the concentrations employed. Sensory anesthesia was considered adequate for surgery in all but one patient. In one patient in whom the 0.75% solution was employed significant amounts of supplemental opioid administration were required in order to provide adequate surgical anesthesia intraoperatively. The average maximum whole blood venous concentration of ropivacaine increased from 0.43 ug/ml with 100mg of ropivacaine to 0.95 ug/ml when 200mg of ropivacaine was injected epidurally. No signs of systemic toxicity were observed in any of the patients.

Discussion. These preliminary human studies suggest that epidural ropivacaine produces an acceptable onset and depth and a prolonged duration of sensory anesthesia. The 0.5% concentration demonstrates differential sensory and motor blockade. Increases in concentration resulted in a more profound degree of motor blockade. Ropivacaine may represent a suitable alternative to the use of bupivacaine. However, additional clinical studies are required to determine the ultimate usefulness of this new local anesthetic agent.

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EPIDURAL ANESTHESIA WITH ROPIVACAINE

	CONCENTRATION		
	0.5%	0.75%	1.0%
N	5	5	5
AGE	42 ± 7	35 ± 6	30 ± 8
ONSET TO T_{12}	6.6 ± 1.7	6.4 ± 2,5	2.4 ± 0.6
AVE. MAX. SPREAD	T_6	T_3	T_1
2-SEGMENT REGRESSION	165 ± 25	164 ± 22	157 ± 25
REGRESSION TO T_{12}	255 ± 33	298 ± 21	356 ± 34
COMPLETE REGRESSION	378 ± 38	396 ± 34	438 ± 52
AVE. MAX. MOTOR BLOCK	0.8 ± 0.4	2.0 ± 0.3	2.0 ± 0
ADEQUATE ANESTHESIA	100%	80%	100%

Title: EVALUATION OF A FORCED-AIR PATIENT WARMING SYSTEM FOR HYPOTHERMIC POSTSURGICAL PATIENTS

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Introduction. Despite efforts at prevention, 60-85% of adult postsurgical patients are hypothermic (temperature $<$ 36°C) upon admission to the recovery room.(1) Elderly patients are particularly at risk.(2) Severe hypothermia (temperature $<$ 30°C) can result in life-threatening ventricular irritability. More commonly, postoperative hypothermia is not life threatening but constitutes an added physiologic stress. If a patient is unable to compensate for the increased metabolic demands, arterial hypoxemia, metabolic acidosis, and cardiovascular instability can result. An effective means of rewarming hypothermic postsurgical patients would decrease the incidence and duration of shivering and minimize the physiologic stress it imposes. We undertook this study to compare the Bair Hugger System™ (BHS)* for rewarming hypothermic postsurgical patients to our conventional method using warm cotton blankets.

Methods. Approval of the Institutional Review Board and informed consent was obtained. Upon entry to the PAR, 15 adult postsurgical patients (age 18-70), who had received general anesthesia and had an oral temperature (Diatech model 600) of $<$ 35°C were randomly allocated by lottery in two groups. Excluded from the study were those patients who were febrile, infected, receiving blood products, hemodynamically unstable, on vasoactive drugs, or intubated, as well as those with underlying muscle, CNS or autonomic nervous system disorders. Group I patients were warmed by warm cotton blankets and group II by the BHS. Oral and axillary temperatures and presence of shivering were noted upon entering the recovery room and every 15 min thereafter until reaching 36°C oral or axillary. The mean rate of temperature rise "± standard deviation", presence or absence and duration of shivering, number of blankets used to warm the patients, and total recovery room time were compared between the two groups. Data was analyzed with an unpaired t test. P value < 0.05 is significant.

Results.

Table 1: Oral Temperature

	Bair			Cotton Blanket		
Time (min)	Mean Temp (°C)	SD	N	Mean Temp (°C)	SD	N
0	34.60	0.76	8	33.77	1.23	7
15	34.87	0.80	9	33.94	0.90	7
30	35.02	0.69†	9	33.74	1.04†	7
45	35.21	0.95†	9	34.13	0.81†	7
60	35.61	0.63†	9	34.43	0.96†	7
75	35.71	0.52†	7	34.70	0.96†	7

Time = min in recovery
SD = standard deviation
N = number of patients
† = $p < 0.05$ between groups

Table 2: Axillary Temperature

	Bair			Cotton Blanket		
Time (min)	Mean Temp (°C)	SD	N	Mean Temp (°C)	SD	N
0	33.97	0.67	9	33.31	0.70	7
15	34.41	0.73	8	33.79	0.75	7
30	34.89	0.58†	9	33.94	0.65†	7
45	35.32	0.82†	9	33.99	0.81†	7
60	35.67	0.99†	9	34.50	0.72†	7
75	35.64	0.56†	7	34.76	0.73†	7

Time = min in recovery
SD = standard deviation
N = number of patients
† = $p < 0.05$ between groups

Discussion. 1) The BHS provided a greater mean rate of temperature rise as compared to warm cotton blankets from 30-75 min at 15 min intervals. 2) Patients were subjectively much more comfortable when the BHS was utilized as compared to warm cotton blankets. Recently it has been postulated that shivering is triggered by cutaneous receptors that respond to skin (but not body) temperature.(3) Our study suggests that the forced-air patient warming system provided a greater rate of temperature rise than warm cotton blankets in the warming of hypothermic postsurgical patients.

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*The BHS consists of a disposable patient cover and a heat source. The cover is made of plastic and tissue paper bonded into tubular channels that contain slits through which warm air will flow next to the patient. The heat source consists of a blower, a 400-watt heating element, and a microprocessor-based temperature control with a maximum temperature limit of 110°F. Prior to circulation through the cover, the air is filtered by a 5 micron filter. The BHS has been approved by the FDA as a class II medical device. Augustine Medical Inc., 10393 West 70th Street, Suite 100, Edina, MN 55344

TITLE: EFFECT OF MAGNESIUM AND CALCIUM ON MYOCARDIAL FUNCTION POST-CARDIOPULMONARY BYPASS

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Introduction. Calcium chloride has been utilized near the termination cardiopulmonary bypass (CPB) in an effort to counteract the negative effects of cardioplegia, hypothermia, and hemodilution have on myocardial contractility.[1] Magnesium on the other hand, has recently been receiving increased use during CPB following reports that it may potentiate the effects of potassium cardioplegia by controlling influx of extracellular calcium through membrane channels.[2,3] The purpose of this study was to compare the effects of magnesium and calcium on myocardial function post-cardiopulmonary bypass.

Methods. Twenty patients scheduled for elective coronary artery bypass surgery were studied after obtaining institutionally approved informed consent. Cardiac medications were continued up until the morning of surgery. All patients received lorazepam (1-2 mg PO), morphine (0.1 mg/kg IM), and scopolamine (0.3 - 0.4 mg IM) two hours prior to the induction of anesthesia. Patients were monitored utilizing a two-lead electrocardiogram, and a central venous, pulmonary artery, and radial artery catheter. Anesthesia was induced with fentanyl (50 µg/kg IV), and lorazepam (4 mg IV). Muscle relaxation was facilitated by a metocurine (0.1 mg/kg IV), pancuronium (0.025 mg/kg IV) combination. Patients were randomly assigned to two groups. Group 1 patients had 4 grams of magnesium sulphate (Mg^{++}) placed in a 1500 ml crystalloid pump prime. Group 2 patients received 1 gram of calcium chloride (Ca^{++}) in to the CPB pump once the heart began contracting following the removal of the cross clamp. The conduct of the anesthesia and surgery was otherwise the same in each group. Hemodynamic measurements were obtained following anesthetic induction, pre-CPB prior to placement of cannulae, post-CPB once stable following protamine administration and, lastly after chest closure. Measurements obtained include heart rate (HR), systemic blood pressure (SBP), pulmonary artery pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), stroke index (SI), left and right ventricular stroke index (LVSWI, RVSWI) were calculated from the above data. Analysis of the data was performed using Student's t-test for unpaired data and one way analysis of variance with significance set at $p < 0.05$.

Results. Results for the Mg^{++} and Ca^{++} groups are shown in Table 1 and Figure 1. The data shows that SI and RVSWI were significantly lower in the Ca^{++} group post-CPB and at chest closure. LVSWI was significantly lower in the Ca^{++} group at chest closure. The groups did not significantly differ with respect to any preoperative variables, or any other hemodynamic variable measured at any of the four measurement time points.

Discussion. Calcium administration at the end of CPB has decreased recently due to the fact that other inotropic agents exist which are more effective and that calcium may contribute to the generation of coronary artery spasm and ischemia.[4] The evidence continues to mount, however, with respect to the beneficial effects of magnesium in the pump prime and/or cardioplegic solution.[2,3] The data elucidated by this study reveal that myocardial performance following CPB is significantly better in those patients who received Mg^{++} in the pump prime compared to those who received Ca^{++} at the end of CPB.

From these findings, we conclude that, calcium chloride should not routinely be used at the termination of CPB. Additionally, further study is necessary to elucidate the beneficial effects of magnesium sulphate in the pump prime.

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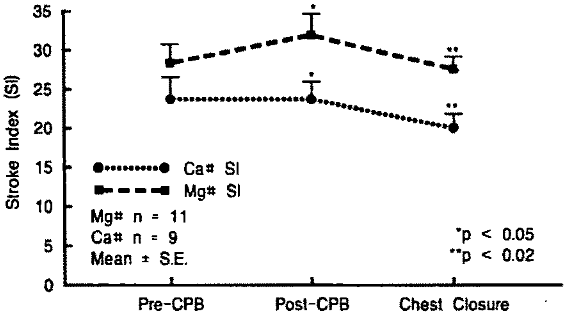
TABLE 1

Mg# Vs. Ca#

		Pre-CPB	Post-CPB	Chest Closure
Stroke Index	Mg#	28.4±2.4	32.0±2.7*	27.6±1.6**
	Ca#	23.7±2.9	23.7±2.3*	20.0±1.8**
LVSWI	Mg#	29.2±2.6	27.4±1.7	24.7±1.7**
	Ca#	23.4±3.6	23.5±2.1	17.9±1.7**
RVSWI	Mg#	3.1±.93	5.3±.66**	4.1±.48*
	Ca#	2.8±0.5	2.7±0.4**	2.6±0.5*

Mg# n = 11
Ca# n = 9 $^{*}p < 0.05$
Mean ± S.E. $^{**}p < 0.02$

FIGURE 1



TITLE: POST-INDUCTION HEMODYNAMIC RESPONSES OF PATIENTS IMPLANTED WITH THE JARVIK-7 TAH

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Introduction. The hemodynamic effects of even the most thoroughly understood anesthetic agents are virtually unknown in the TAH recipient. We investigated the central and peripheral vascular effects of four commonly used short-acting anesthetic agents in human recipients of the Jarvik-7 TAH.

Methods. Four human subjects with the Jarvik-7 TAH in situ and requiring intervention composed the study population. When clinically appropriate, and following the collection of baseline hemodynamic information, these patients were induced with a rapid bolus injection of one of four anesthetics: sufentanil (SUF; 10 μg/kg), sodium thiopental (STP; 5 mg/kg), ketamine (KETA; 2 mg/kg), or etomidate (ETOM; 0.3 mg/kg). Anesthetic induction, in all cases, was accompanied by the administration of vecuronium (0.1 mg/kg). Following induction, hemodynamic (SBP, DBP, MBP, RCO, LCO, CVP) and pulmonary function (TV, EtCO$_2$, FiO$_2$, O$_2$SAT, VR, WKIN, CMP, RES) variables were recorded at intervals of 2, 5, and 10 minutes. Artificial heart drive parameters (HR, RDP, LDP, %SYS, VAC) were held constant during the study period so that any observed hemodynamic responses were solely attributable to changes in the pulmonary and systemic vasculature. This protocol was approved by the Human Subjects Committee, and written informed consent was obtained from each patient.

Results. Results are summarized in the accompanying table.

Sufentanil (SUF): Approximately 2 minutes following SUF induction, a transient elevation in both LCO (5.05 L/min to 5.28 L/min) and RCO (5.31 L/min to 6.66 L/min) was noted. The duration of this elevation was approximately 5 min.

Sodium Thiopental (STP): Both LCO and RCO remained stable during the 10 min. post-induction study period. LCO and RCO changed by -4% and 0% respectively following STP induction. MBP decreased 92 mmHg baseline to 63 mmHg pre-intubation.

Etomidate (ETOM): While RCO and LCO were consistent during the study period (+5% and 1.5% changes, respectively), both MBP and SVR exhibited oscillations from low to high values. MBP ranged from a low of 61 mmHg to a high of 104 mmHg, and SVR varied between a low of 512.2 dynes-sec/cm^5 to a high of 925.3 dynes-sec/cm^5. These oscillations were transient as the MBP and SVR responses returned to baseline values at the conclusion of the 10 min. study period.

Ketamine (KETA): Ketamine induced predictable hemodynamic perturbations in the TAH patient. Both LCO and RCO rose slightly during the study period from baseline values of 6.59 L/min and 8.27 L/min to final outputs of 7.03 L/min and 9.09 L/min respectively. This response was accompanied by a +14% change in MBP.

Discussion. Hemodynamic responses to SUF, STP, ETOM, and, to a lesser degree, KETA inductions in the TAH recipient differ markedly from those reported by a variety of authors investigating the same effects in patients having an intact circulations. These discrepancies indicate need for further understanding of the isolated cardiac and vascular effects of these agents. For example, contrary to published results, SUF showed a net increase in MBP and SVR in the TAH patient. Reported findings indicate an expected decrease in MBP and SVR.[1] Similarly, in the intact circulation STP has been shown to cause a transient increase followed by a fall in SVR and decreases in both CO and MBP.[2] While our findings substantiate the MBP response, their implications for SVR disagree with those reported for the intact circulation. ETOM is purported to cause the least perturbation of hemodynamic performance in the intact circulation of any of the agents that we examined.[2] Indeed, ETOM's effect on CO in the TAH recipient was negligible, as expected, but the oscillations it generated in the MBP and SVR responses were far from minimal. Lastly, the results obtained for KETA induction appeared to be the most consistent with the hemodynamic responses published in the literature.[2] KETA appears to have properties that are predictable in both the intact human circulation and that containing a TAH, although more study needs to be done.

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TABLE 1

Hemodynamic Responses of TAH Recipients to Anesthetic Induction

AGENT	TIME (min) 0	2	5	10
Sufentanil (n=1)				
RCO (L/min)	4.85	5.31	6.65	5.04
LCO (L/min)	4.80	5.05	5.26	4.95
MBP (mmHg)	74	94	96	119
SVR*	1137.2	1071.2	1096.2	1553.4
Sodium Thio. (n=1)				
RCO (L/min)	8.09	8.01	8.03	8.09
LCO (L/min)	7.27	7.45	7.39	6.97
MBP (mmHg)	92	91	88	63
SVR	na	na	na	na
Etomidate (n=1)				
RCO (L/min)	7.44	7.40	7.41	7.75
LCO (L/min)	6.23	6.37	6.19	6.57
MBP (mmHg)	70	61	104	78
SVR	670.6	512.2	925.3	689.8
Ketamine (n=1)				
RCO (L/min)	8.27	8.88	9.32	9.09
LCO (L/min)	6.59	6.95	7.24	7.03
MBP (mmHg)	86	101	100	100
SVR	na	na	na	na

*SVR in units of dynes-sec/cm^5

Title: CONTRIBUTION OF HYPOXIC VASOCONSTRICTION TO MATCHING OF VENTILATION AND PERFUSION IN DOGS

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Introduction: Pulmonary vascular constriction in response to low oxygen tension (HPV) has been the subject of intense investigation. HPV is thought to be responsible for both protection from hypoxemia during atelectesis and the right ventricular failure associated with diffuse pulmonary disease. However, the contribution of HPV to normal distribution of blood flow (Q) within the lung and the matching of ventilation to lung blood flow (V/Q) during air breathing is unclear. This study was designed to define the contribution of HPV to V/Q.

Methods: Ten dogs (17-20 kg) were anesthetized with barbiturate (pentobarbital 30 mg/kg and maintained by infusion, 5 mg/kg/hr) and muscle paralysis (pancuronium 0.2-0.5 mg/kg every hour). After double-lumen endobronchial intubation, isolation of the right and left lung was verified by the absence of cross contamination of expired gas during unilateral ventilation with a helium containing mixture. Percutaneously placed cannulae allowed measurement of systemic arterial, central venous, pulmonary arterial, and pulmonary artery occlusion pressures. Thermodilution cardiac outputs were obtained and pulmonary vascular resistance was calculated.

A dual-piston ventilator provided synchronous ventilation of both lungs, with tidal volumes and frequency selected to maintain normal bilateral end-tidal P_{CO2}. The distribution of V/Q was assessed using the multiple inert gas elimination technique (1). Inert gas concentrations in arterial and mixed venous blood and mixed expired gas samples were measured by gas chromatography. The plot of the ratio of mixed arterial to mixed venous gas concentrations against solubility was constructed using the above data. This curve was then transformed to a distribution of Q to V/Q ratio by digital computer algorithm assuming a lung model with 50 V/Q compartments (V/Q range, 0.005 to 100) (1).

After short trials of hypoxic ventilation alternating with 100% O2 ventilation resulted in stable, reproducible pulmonary arterial pressure responses to hypoxia (2), the subsequent study was divided into five experimental conditions. Condition 1 (C-1), 100% O2 ventilation bilaterally, provided control hemodynamic variables and V/Q distribution during minimal HPV. Condition 2 (C-2), inspired O2 of 80 mmHg bilaterally, was designed to insure low alveolar O2 tension in lung segments of low V/Q. Condition 3 (C-3) maintained the hypoxic stimulus of C-2 but sodium nitroprusside (SNP) was infused (10-30 ug/kg/min) to abolish HPV. Condition 4 (C-4), decreased tidal volume in the left lung (f and mean airway pressure constant), was designed to increase the proportion of the lung segments with low alveolar O2 tension secondary to low V/Q. Condition 5 (C-5) maintained the same challenge as C-4 as SNP was infused to abolish HPV. The order of C-2, C-3 and C-4, C-5 pairs was alternated on sequential study subjects.

For each study condition a mean value of Q at each of the 50 compartments was calculated using these data for the entire study population. Curves of mean values plotted against V/Q were compared using Kolmogorov-Smirnov goodness of fit for continuous data. Additionally, the mean percent of total Q to compartments of low V/Q (shunt + V/Q <0.1) for each condition were compared by one way analysis of variance for repeated measures.

Results: Calculated pulmonary vascular resistance significantly increased during C-2 and C-4 and decreased to control (C-1) values during SNP infusion (C-3 and C-5). Percent Q to compartments of low V/Q increased significantly (p<.05) during C-5. The distribution of Q to V/Q during C-2 and C-3 did not differ from each other or C-1 (Fig.1). Conversely, the Q to V/Q distribution during C-4 and C-5 differed significantly from C-1 and from each other (P<.001) (Fig.2).

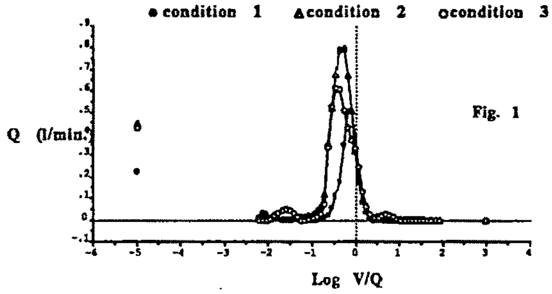

Fig. 1

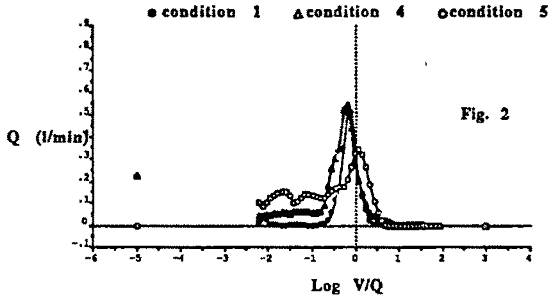

Fig. 2

Discussion: This study suggests that in the dog, HPV limits Q to compartments of very low V/Q but other factors (gravity, lung architecture, diffusion) are responsible for the normal narrow distribution of Q to V/Q compartments (V/Q values 0.5 to 2.0). Recent evidence suggests that the pulmonary vascular response to hypoxemia may be less vigorous in dogs than in humans or swine (3). Additionally, we speculate that the Q distribution during C-2 and C-3 did not from C-1, despite significant HPV, because the hypoxic inspired mixture resulted in a severe, global, stimulus for constriction rather than widening the range of alveolar O2 tensions associated with V/Q compartments as intended.

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Title: RECURRENT HERPES SIMPLEX VIRUS LABIALIS IN PARTURIENTS RECEIVING EPIDURAL MORPHINE

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Introduction. A significant association between reactivation of Herpes simplex virus labialis (HSVL), facial pruritus, and the use of epidural morphine (EM) in obstetric patients has been reported[1,2]. Our initial studies[1] identified a number of potential confounding variables such as surgical stress, the use of epinephrine, and local anesthetics. We therefore designed a prospective, randomized study of parturients having cesarean sections (C/S) with epidural anesthesia to eliminate these possible confounders.

Methods. Following approval by our institutional ethics committee and with informed consent, patients having C/S with epidural anesthesia were sequentially randomized immediately following delivery to receive either EM or intramuscular (IM) narcotics for postoperative pain control. Surgical anesthesia was achieved with carbonated lidocaine with 1:200,000 adrenalin. One blood sample was obtained for viral serology, and two mouthwashes were collected to determine oral viral shedding, on the day of surgery and the 2nd postoperative day. Postoperatively, patients were observed daily for five days and clinically evident cold sores were cultured for HSV. Statistical analyses for discrete variables were performed using chi-square and the Fisher exact test with $P<0.05$ considered significant.

Results. Of 187 patients enrolled, 96 received epidural morphine and 91 IM narcotics. There was no significant difference between the groups with respect to age, parity, number of coldsores in the present pregnancy, previous history of coldsores, ASA physical status, the urgency of surgery, or the frequency of seropositivity to herpes simplex virus. Fourteen of 96 (14.6%) receiving EM developed oral HSVL lesions (coldsores) compared to 0 of 91 having IM narcotics ($p=0.0004$). Facial pruritus occurred in 71 of 96 (78%) patients having EM compared to 12 of 91 (13.2%) in the IM group ($p<0.001$). All 14 patients with recurrent HSVL lesions experienced facial pruritus ($p<0.001$). Sixty-two of 96 (64.6%) patients having EM and 57 of 91 (62.6%) in the IM group were seropositive to the Herpes simplex virus. Oral viral shedding was detected in 10 patients, 2 of whom developed HSVL lesions.

Discussion. Elimination of all but one previously described confounders in this study supports the hypothesis of a significant association between HSVL reactivation, occurrence of pruritus and the use of epidural morphine in pregnant patients. Naloxone was administered intravenously to patients with pruritus and remains a potential though unlikely confounder. The incidence of oral viral shedding was low and was not useful in predicting HSVL reactivation. The mechanism of reactivation is yet unknown and purely speculative. We suggest it may be related to a central stimulation of the trigeminal nerve ganglion by the epidural morphine, inducing pruritus and mobilization of the latent herpes virus.

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TITLE: SPINAL BLOOD FLOW DURING TETRACAINE SPINAL ANESTHESIA IN CONSCIOUS RATS

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AFFILIATION: From the Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts

INTRODUCTION

Tetracaine spinal anesthesia is prolonged by addition of epinephrine,[1] a phenomenon that could be explained either by epinephrine's vascular or analgesic effects. Evidence for the former comes primarily from one study[2] which indicates that epinephrine prevents a tetracaine-induced increase in spinal cord blood flow (SCBF). However, spinal anesthesia with other local anesthetics reduces SCBF[3] and subarachnoid epinephrine alone is probably not a vasoconstrictor.[4] Consequently, we questioned the hypothesis that epinephrine restores to normal SCBF increased by subarachnoid tetracaine.

METHODS

This study received institutional approval. Spinal blood flow was measured in conscious rats that received either saline (n = 5), tetracaine (n = 5), or tetracaine plus epinephrine (n = 5), through chronically implanted lumbar subarachnoid catheters.[3] On the day of experiments, animals were anesthetized briefly with halothane-nitrous oxide for insertion of femoral artery and vein catheters. Animals were then partially immobilized with a pelvic plaster cast and allowed to awaken for at least 2 hr. Drugs were prepared and administered in saline 10 ul. Control rats received saline only while others received tetracaine 200 ug, with or without epinephrine 8 ug, intrathecally. Mean arterial blood pressure (MAP) and blood gases were measured and rectal temperature was controlled with a heat lamp. Analgesia was assessed with the tail-flick test.

SCBF was measured in the lumbar spinal cord with the autoradiographic iodo-$[^{14}C]$antipyrine method 15-20 min after subarachnoid drug administration.[3] Data were analyzed by Bonferroni's test for multiple comparisons.

RESULTS

Spinal anesthesia reduced MAP slightly (106 ± 7 vs 118 ± 4 mm Hg, $P > 0.1$) and had no effect on other physiologic variables. MAP was lower (85 ± 6 mm Hg, $P < 0.05$) in rats treated with tetracaine plus epinephrine. Tetracaine alone made the tail flaccid and abolished spontaneous movement but did not prolong the tail flick. Tetracaine plus epinephrine produced maximal analgesia. Subarachnoid tetracaine reduced SCBF dramatically and the decrease was greater in spinal gray (45-60%) than in white matter (20-30%) (Table). SCBF decreased further when epinephrine was added to the solution (Table). However, this difference was statistically significant in only two areas and, when MAP was restored to normal with phenylephrine (n = 5, data not shown), SCBF returned to levels found with tetracaine alone.

TABLE

SPINAL BLOOD FLOW ($\mathrm{ml \cdot 100g^{-1} \cdot min^{-1}}$)

	Control (5)	Tetracaine (5)	Tetracaine + Epinephrine (5)
GRAY MATTER Lamina(e)			
I - III	62 ± 2	33 ± 3 †	21 ± 2 †§
IV - VI	90 ± 8	39 ± 5 †	27 ± 3 †
VII	120 ± 7	45 ± 5 †	33 ± 3 †
VIII	114 ± 4	44 ± 5 †	32 ± 3 †
IX	105 ± 4	38 ± 4 †	27 ± 3 †
WHITE MATTER			
Dorsal	27 ± 3	22 ± 3 †	14 ± 2 †
Lateral	40 ± 3	27 ± 3 †	17 ± 2 †‡
Ventral	33 ± 2	24 ± 3 *	17 ± 2 †

Data are mean ± SEM.
* $P < 0.05$ and † $P < 0.01$ compared to control;
‡ $P < 0.05$ and § $P < 0.01$ compared to tetracaine.

DISCUSSION

We conclude that in conscious rats tetracaine spinal anesthesia profoundly reduces SCBF. While addition of epinephrine enhanced the anesthetic effect of tetracaine, SCBF was not decreased substantially more, provided MAP was maintained. Subarachnoid bupivacaine also reduces SCBF,[3] but tetracaine has been reported to increase[2] or not alter it.[3] Species differences, use of saline rather than 10% dextrose as a vehicle, or the fact that previous studies[2,3] were performed in anesthetized animals, could explain these discrepancies. Nevertheless, these data challenge the hypothesis that epinephrine prolongs spinal anesthesia by preventing tetracaine-induced spinal vasodilation.

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Title: RETROBULBAR BLOCK: EFFECT OF HYALURONIDASE ON LIDOCAINE SYSTEMIC ABSORPTION AND CSF DIFFUSION IN DOGS.

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INTRODUCTION Serious and potentially lifethreatening complications reported following retrobulbar injections of local anesthetic agents include respiratory arrest, brain stem anesthesia, grand mal seizures and transient bilateral blindness[1]. Inadvertent intravascular injection of local anesthetic agent, intra-arterial injection with retrograde flow and spread in the internal carotid artery distribution and optic nerve sheath injection with central spread into the subarachnoid and subdural spaces, have all been proposed as mechanisms for these untoward reactions[2]. Hyaluronidase is added to local anesthetic agents for retrobulbar block to hasten onset and to provide more effective orbicularis and extraocular muscle akinesia[3].

This study was undertaken to determine (i) the systemic absorption and CSF diffusion of lidocaine following a standard local anesthetic technique for retrobulbar and facial nerve block used for ophthalmic surgery and (ii) the effect of hyaluronidase, added to the local anesthetic, on lidocaine levels measured.

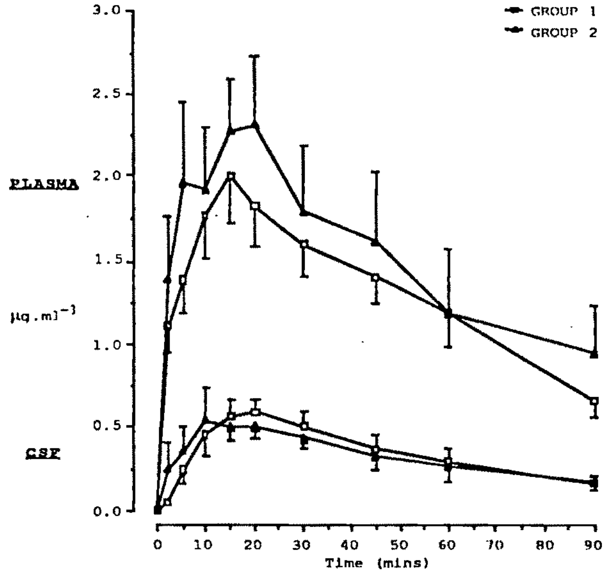
METHODS Following institutional research committee approval, 12 greyhounds (weight 20-30 kg) were randomly allocated to two groups. Group 1 (N=6) received local anesthetic solution containing 1% lidocaine with epinephrine 1/200,000. Group 2 (N=6) received 1% lidocaine with epinephrine 1/200,000 and hyaluronidase 5 units/ml.

Anesthesia was induced with sodium pentothal 20 mg/kg and maintained with N_2O/O_2 60/40% and 0.5-1% halothane. Following endotracheal intubation, controlled normocapnic ventilation was instituted. The femoral artery was cannulated for direct arterial pressure monitoring and arterial blood sampling. A 22g spinal needle was located in the cisterna magna to facilitate CSF sampling. Continuous ECG, arterial pressure, end-tidal CO_2 and temperature recordings were obtained.

8ml of local anesthetic was injected - 2ml as a retrobulbar injection for intraocular anesthesia, 2ml for upper eyelid anesthesia and 4 ml for extraorbital facial nerve blockade (van Lint technique). Correct needle placement with retro- bulbar technique was confirmed by dye injection and anatomic dissection. Arterial blood (10 ml) and CSF (1.5 ml) samples were taken prior to and 2, 5, 10, 15, 20, 30, 45, 60 and 90 minutes following local anesthetic injection. Plasma and CSF lidocaine levels were measured using a gas chromatographic technique. The data is reported as mean ± SEM. Statistical analysis was performed using repeated measures analysis of variance and Student's t test. $P<0.05$ was considered significant.

RESULTS The hemodynamic, respiratory and temperature recordings obtained remained stable throughout the study period. Peak plasma lidocaine levels achieved were 2.49 ± 0.33 µg/ml in Group I and 2.23 ± 0.23 µg/ml in Group 2. Peak plasma levels were measured at 15-20 minutes in both groups. There were no statistically significant differences in plasma levels between the groups at any of the sampling times. (Fig 1) Peak CSF lidocaine levels achieved were 0.644 ± 0.079 µg/ml in Group I and 0.647 ± 0.122 in Group 2 and occurred between 10 and 30 minutes in Group 1 and 15 and 30 minutes in Group 2. CSF levels in the two groups were not significantly different at any time.

FIGURE 1: LIDOCAINE CONCENTRATIONS



DISCUSSION The addition of hyaluronidase to 1% lidocaine in epinephrine 1/200,000 solution, in a standard dose and technique for ophthalmic surgery, did not increase the systemic absorption and CSF concentration of lidocaine in this study. Hyaluronidase should not, therefore, be implicated as an etiological factor in CNS toxicity. The peak CSF lidocaine levels measured following correctly placed retrobulbar injection in this study were very much lower than the levels reported in association with respiratory arrest and brain stem anesthesia[4]. Peak CSF lidocaine levels were recorded 10-30 minutes following retrobulbar injection in this study while most clinical CNS toxicity reactions occured 2-8 minutes following injection. Inadvertent injection of local anesthetic into the optic nerve sheath may be the most likely mechanism of untoward reactions following retrobulbar block.

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Title: Systemically Administered Clonidine Enhances Postoperative Epidural Opiate Analgesia.

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Introduction. Electrophysiological (1) and behavioral (2) studies and a clinical report (3) have shown potentiation of morphine analgesia by clonidine. This interaction occurs at the spinal cord level (1,3), a central mechanism appears to be involved as well. Therefore, the administration of clonidine to a patient receiving epidural opiates may provide superior analgesia and/or allow for a reduction of opiate requirement, thus decreasing the risk of respiratory depression. The present study evaluated the effect of systemically administered clonidine (SAC) on post-operative analgesia obtained by the epidural narcotics.

Methods. Institutional Review Board approval and patients' informed consent were obtained. Patients scheduled for either upper abdominal surgery (UAS) or total hip arthroplasty were assigned to either Group I (control, n=10), or Group II (clonidine, n=14), according to a randomized double blind, placebo controlled design. Approximately 90 min prior to surgery, Group II received clonidine 5 mcg/kg po and 4-5 mcg/kg by transdermal patch to maintain clonidine levels achieved by the oral dose. Group I received diazepam 0.1 mg/kg po preoperatively. All patients had an epidural catheter placed at L2-L3 or L3-L4 preoperatively and a combined epidural-general anesthetic technique was employed. Epidural morphine was given intraoperatively at least 45 min prior to extubation in an attempt to provide adequate analgesia by the time of emergence from anesthesia. The dose was chosen based on the site of surgery and the age of the patient. In the UAS patients, fentanyl (50 mcg epidurally) was also given. Level of pain was assessed by a visual analogue pain scale (VAPS) within 15 min of extubation (T0) and 1, 2, 3, 4, 8, and 24 hours afterwards. Supplemental doses of epidural opiate were administered as required to obtain a VAPS of 3 or lower. FEV$_1$, FVC and PEFR measurements were obtained in the UAS patients. Cardiovascular variables and side effects were also recorded at the above intervals. Data were compared between groups using chi-square analysis and by Fischer's exact test.

Results. There was no difference between the two groups with regards to demographics, type of surgery, the amounts of intraoperative intravenous fentanyl, isoflurane, epidural lidocaine and morphine given, and in the interval between the last doses of iv narcotic and the time of extubation. Postoperative epidural narcotic requirements were also similar. At T0, the clonidine group experienced better analgesia, 71.4% of the patients had a VAPS of 3 or less and only 7.1% experienced severe pain or a VAPS > 7, as compared to 50% and 30% respectively in Group I. (P<.05) (see figure). Moreover, 3 control patients had a VAPS of 10 while only 1 patient in the clonidine group had a VAPS greater than 5 at T0. Compared to controls, the clonidine group had a mild but statistically significant decrease in SBP and increase HR at T8 and T24. Pulmonary function tests did not differ between groups and did not correlate with pain scores. No respiratory depression requiring treatment occurred.

Discussion. Clonidine administered systemically appears to enhance epidural opiate analgesia only in the early postoperative period. This may have occurred secondary to falling clonidine levels owing to inadequate drug delivery to maintain a sufficient plasma concentration, thus adequate binding to spinal cord alpha-2 receptors was not sustained. Conversely, the early effectiveness of clonidine may have been caused by potentiation of the residual anesthetic drugs (i.e. fentanyl, isoflurane) that without the presence of clonidine, would have been subanalgesic. This would suggest that systemically administered clonidine does not achieve significant activation of spinal alpha-2 adrenoreceptors but rather potentiates the central action of iv administered opiates and of potent inhalation agents. The epidural route of administration, therefore, may be to preferable to obtain potentiation of narcotic analgesia. Clonidine premedication has been shown to be effective in decreasing postoperative hypertension, tachycardia and plasma catecholamines (4). The present result demonstrates that clonidine, in addition, reduces the incidence of severe pain on emergence from anesthesia. This may be of particular value in patients with coronary artery disease to suppress deleterious hyperdynamic cardiovascular responses to pain.

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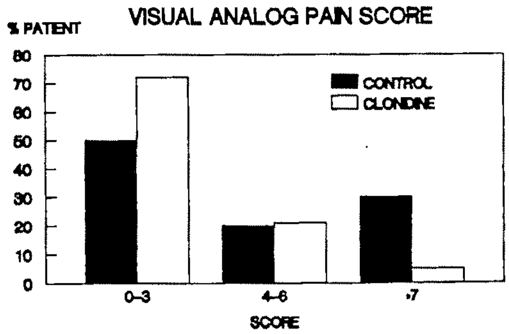

Title: EVALUATION OF PATIENTS WITH PULMONARY HYPERTENSION FOR ORTHOTOPIC HEART TRANSPLANTATION: NITROPRUSSIDE VS. ISORBIDE DINITRATE

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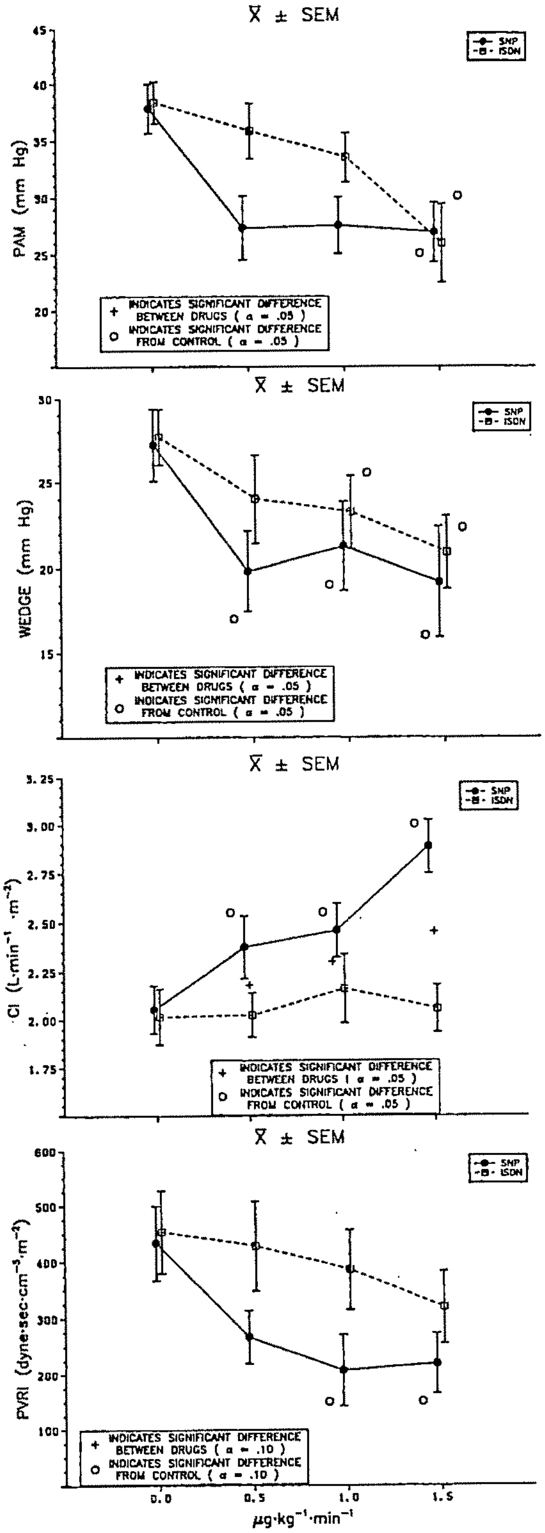
Introduction: When patients with end-stage cardiomyopathies are evaluated for orthotopic or heterotopic heart transplantation, pulmonary hypertension (PH) responsive to vasodilator therapy may allow orthotopic heart transplantation (OHT). Primary or fixed pulmonary hypertension unresponsive to vasodilator therapy mandates heterotopic heart or heart-lung transplantation. A major limiting factor when weaning from cardiopulmonary bypass (CPB) after OHT is right heart failure when the newly transplanted, ischemic heart is suddenly presented with increased impedance, i.e. pulmonary hypertension. The Stanford criteria for OHT requires pulmonary artery systolic (PAS) $\leq$ 50 mm Hg, pulmonary artery mean (PAM) $\leq$ 30 mm Hg and pulmonary vascular resistance (PVR) $\leq$ 320 dyne.sec.cm^{-5} after infusion of sodium nitroprusside (SNP)[1]. The purpose of this study was to evaluate and compare isorbide dinitrate (ISDN) with SNP.

Methods: With the approval of the Human Investigation Committee and after informed written consent, ten awake patients with PH were cannulated with radial artery and thermodilution pulmonary artery catheters. Hemodynamic measurements and calculations were made after progressive infusions of SNP (0.0, 0.5, 1.0 and 1.5 ug.kg^{-1}) and then ISDN (0.0, 0.5, 1.0 and 1.5 ug.kg^{-1}). All patients were at rest, without premedication normocarbic, normoxic and with normal pH. Analysis of variance and Tukey Pair wise comparison were used for data analysis.

Results: (See Figures) SNP and ISDN equally reduced PAM and PCWP. SNP increased CI, decreased mean arterial pressure (MAP) and PVRI whereas there was no change in CI, MAP and PVRI with ISDN.

Discussion: Even though PAM and PCWP were equally reduced by SNP and ISDN, PVRI was not decreased by ISDN because there was no concomitant increase in CI as there was with SNP. In this group of potential heart transplant recipients with significant PH, ISDN had the advantage of selectively lowering pulmonary artery pressures without the decrease in systemic blood pressure observed with SNP and nitroglycerin.[2,3] This suggests ISDN may also offer a therapeutic advantage over SNP and nitroglycerin in the management of patients with persistent PH after orthotopic heart transplantation.



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Title: GLYCOPYRROLATE MAY CROSS THE HUMAN PLACENTAL BARRIER

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Introduction. Several investigators confirmed that atropine crosses the human placenta and causes fetal tachycardia. Since glycopyrrolate is a quaternary ammonium compound, it is unlikely that it would freely cross the placenta. A recent study by Abboud, et al. confirmed that after maternal glycopyrrolate administration, fetal heart rate showed no increase in contrast to atropine. This study was undertaken because transplacental transfer of glycopyrrolate has not been studied in humans and because the technology (R.I.A.) for glycopyrrolate level determination became available.

Methods. Fourteen PS I-II patients undergoing elective cesarean section were studied. Their mean age ± S.E.M. was 23.4 ± 1.4 years, mean weight was 78.3 ± 4.9 kg and height was 158.9 ± 1.2 cm. Premedication consisted of 30 ml of 0.3 M sodium citrate solution p.o. 30 min. prior to operation. All patients received a standard I.V. dose of 0.2 mg of glycopyrrolate within ten minutes of induction of anesthesia. Eleven patients received general endotracheal anesthesia and were induced with thiopental (mean dose of 3.4 mg/kg) and relaxed with succinylcholine (mean dose of 1.3 mg/kg). Three patients received appropriate doses of local anesthetic for epidural anesthesia. Maternal venous blood samples and umbilical cord blood samples were collected simultaneously at the time of cord transection. The samples were assayed in duplicate by radioimmunoassay by the method of Wright, et al. (from Research Laboratories of A. H. Robbins Co. - unpublished data) with a lowest quantifiable limit of 100 pg/ml and a linear distribution from 100 to 3000 pg/ml. The mean time from injection of glycopyrrolate to delivery of the infant was 27.2 min. and varied by ± 4.3 (S.E.M.). IRB approved the study.

Results. The mean ± S.E.M. maternal blood level of glycopyrrolate was 507.2 ± 71.3 pg/ml. Ten neonates had no measurable blood levels at all. Four neonates had levels ranging from 168 to 327 pg/ml. As a consequence for these four patients, the mean ± S.E.M. is not reportable.

Discussion. The transplacental transfer of glycopyrrolate was nil in 10 neonates as would be expected. The measurable levels in the other four neonates may have been caused by a breakdown in the normal placental barrier due to maternal hemodynamic abnormalities such as hypertension or maternal infection. Each individual case will be discussed. In conclusion, transplacental transfer of glycopyrrolate presumably does not occur through an intact placental barrier as is reflected by the ten healthy parturients in whom no measurable amount of glycopyrrolate crossed the placenta. It does occur, however, under certain as yet unidentified conditions as is reflected by the four cases with measurable neonatal glycopyrrolate levels. Further studies on the stability of the placental barrier with respect to quaternary ammonium compounds and factors which may disrupt it are warranted.

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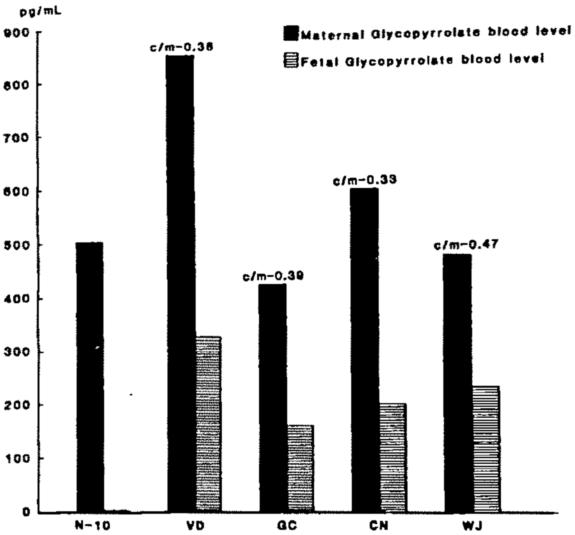

Title: EFFECT OF AGING ON THE INCIDENCE OF MINOR POST ANESTHETIC COMPLICATIONS

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Introduction. Elderly surgical patients may be more susceptible to commonly occurring minor post anesthetic complications which may adversely affect post operative recovery and perhaps prevent early discharge from the hospital. We therefore prospectively investigated in a population of surgical patients who had received general anesthesia if aging had any effect on the occurrence of minor post anesthetic complications and if there was any sex effect on these complications in the elderly. We also investigated in a surgical population treated with spinal anesthesia the effect of aging on the occurrence of post spinal headache.

Methodology. The general anesthesia (GA) population consists of 3032 patients, 1326 men and 1706 women who underwent various surgical procedures excluding cardiothoracic, major vascular and neurosurgical procedures. The patients of these populations were divided in three age groups ranging from 18 to 50 (n=1471), 51 to 70 (n=1141) and 71 to 93 (n=420) years of age respectively. The patients were interviewed by a nurse clinician 24 hours following surgery about the possible presence of any of the post anesthetic problems or complications listed in the table. The spinal anesthesia (SA) population consisted of 437 patients similarly categorized in three age groups consisting of 90, 181 and 166 patients respectively. Criteria for post spinal headache included (1) onset of headache 24-48 hours after surgery; (2) postural character, exacerabated by sitting or standing and (3) occipital or frontal location. Data were submitted to statistical analysis consisting of 3 x 2 contingency tables with Pearson's Chi Square Analysis or Fisher's Exact Test and of testing for linearly increasing trends.

Results. For the GA population, the complication or problem that had the highest occurrence was sore throat (31%), followed by headache (12.5%), muscle pains (11.2%), nausea (11%) and decreased mental alertness (8%) as can be seen from the second column in the table. In the elderly, sore throat (18.3%) had still the highest occurrence rate, followed by decreased mental alertness (9.2%), headache (8.2%), hoarseness (7.2%) and nausea (7%). Looking for a possible sex effect on the incidence of these complications in the elderly, we noticed that decreased mental alertness (14.5% versus 3.1%, $p < 0.01$), nausea (23% versus 6%, $p < 0.01$), complications at the IV puncture site (11% versus 1%, $p < 0.01$) and muscle pains (13% versus 3%, $p < 0.05$) were more frequent in elderly women than in elderly men. Except for decreased mental alertness and for complications at the IV puncture site, we observed a statistically significant age effect on the incidence of all other post anesthetic complications or problems listed in the first column of the table as indicated by an asterisk sign. Testing for a linearly increasing trend with age indicated that only incidences of breathing problems and hoarseness were increasing with age (indicated by a # sign in the fifth column). For the SA population, the overall incidence of post spinal headache was 2% and its incidence in the elderly was 0.6% compared to 1.7% and 7.7% in the younger age groups. (See lower part of table)

Discussion. The incidence of minor post anesthetic complications has been reported in the past (1). However, to our knowledge, a specific search for the effect of age on such complications has not yet been published. Our prospective study shows clearly an age effect on the incidence of many minor post anesthetic complications. It is interesting to note that, while sore throat retained its highest incidence in all age groups, other complications such as muscle pain became much less frequent with advancing age. It is reassuring that only a few of these minor complications have a tendency to increase with age. The function of the respiratory system decreases with age so that there is no surprise to find here an increasing trend in post operative breathing problems. The higher incidence of hoarseness in the elderly could also be part of this problem. However, perioperative hoarseness and tracheal intubation are strongly associated events ($p < 0.01$) so that a higher degree of trauma inflicted to more fragile laryngeal structures by laryngoscopy and/or the endotracheal tube may also be responsible for the higher occurrence of hoarseness in the elderly. Finally, since spinal anesthesia is used so often in the elderly, it is gratifying to observe that the elderly is much less susceptible to post spinal headache than younger individuals.

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Minor Postanesthetic Complications

Age Groups	All ages	18-50 y	51-70 y	71-93 y
General Anesthesia (GA) Population: n=	3032	1471	1141	420
Complication: Incidence (%)				
Breathing problem*	2.1	1.5	1.9	3.9#
Dysphagia*	6.2	7.5	5.1	4.6
↓ mental alertness	8.0	7.7	7.9	9.2
Lip injury*	4.3	6.0	3.0	2.2
Sore throat*	30.9	36.4	28.4	18.3
Hoarseness*	4.8	3.7	6.3	7.2#
Muscle pains*	11.2	14.1	10.1	3.9
Nausea*	11.0	13.7	9.1	7.0
Vomiting*	4.7	6.0	8.0	2.9
Headache*	12.6	13.2	13.2	8.2
IV site complication	5.5	4.6	6.2	6.3

	All ages	18-50 y	51-70 y	71-93 y
Spinal anesthesia (SA) Population: n=	437	90	181	166
Complication: Incidence (%)				
Post spinal headache*	2.0	7.7	1.7	0.6

* $p < 0.05$ by Chi square analysis or Fisher's Exact Test.
# $p < 0.05$ by Linearly Increasing Trend analysis.

Title: MYOCARDIAL ISCHEMIA: A COMPARISON BETWEEN ISOFLURANE AND ENFLURANE DURING CABG SURGERY

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Introduction. There is concern over the use of isoflurane in patients with CAD due to the possibility of ischemia induced via a coronary steal phenomena. Previous studies (1,2) reporting ischemia with isoflurane utilized EKG and myocardial lactate extraction to detect ischemia. They allowed significant drops in MAP and used isoflurane as an induction agent, either of which may have contributed to ischemia independent of any steal phenomena. Our study was designed to determine, in CABG patients receiving a combination narcotic and inhalational anesthetic, if there is any greater incidence of myocardial ischemia in patients receiving isoflurane compared to a group receiving enflurane when MAP is maintained within 20% of baseline.

Methods. This study was approved by the human research review board and patients' written informed consent was obtained. 23 patients scheduled for elective CABG surgery with ejection fractions greater than 45% were randomly assigned to receive 0.7% isoflurane or 0.9% enflurane following intubation; induction of anesthesia was obtained with 25 ug/kg fentanyl and 0.1 mg/kg vecuronium. Patients received their usual cardiac medications and diazepam pre-op. Measurements were made pre-induction (period P1), post-induction (period P2), and after 20 minutes of inhalational agent (period P3)--all prior to incision. Patients were ventilated with a 50/50 mixture of O_2 and N_2. PCO_2 was maintained between 35 and 45 mmHg; MAP was maintained within 20% of baseline with upper and lower limits of 120 mmHg and 50 mmHg; PCW was maintained between 8 and 15 mmHg; heart rate greater than 15% above baseline or above 80 was treated with esmolol; bradycardia was treated only if associated with hypotension. A 7-lead EKG, myocardial lactate extraction, and transthoracic 2-D echocardiography were used to detect myocardial ischemia. Ischemia was defined as the development of new ST segment changes greater than 0.1 mv, or the production of lactate, or new wall motion abnormalities. Transthoracic ECHO sub-costal views of the left ventricle short axis at the mitral, papillary, and apical levels and the left ventricular long axis view were analyzed by two observers unaware of the inhalational agent used. The long axis view was divided into five segments, the mitral and the papillary short axis into eight each, and the apical short axis into four. Each segment was visually graded for systolic wall thickening and motion: +1--hyperkinetic, 0--normal, -1--severe hypokinesis, -2--akinesia, -3--dyskinesia. Ischemia was defined as any deterioration of baseline measurements to -1 or worse; both readers had to agree on gradings. Fishers one-tailed exact test was used to compare incidence of ischemia between agents; repeated measures analysis of variance was used for the hemodynamic measurements.

Results. There was no statistically significant difference in incidence of ischemia between the two groups. Hemodynamic variables were similar in both groups. We were unable to obtain an ECHO in one patient in the enflurane group; the coronary sinus catheter could not be placed in six patients--three in the isoflurane group and three in the enflurane group. See tables one and two.

Discussion. Although several studies (1,2) have shown an association between isoflurane and ischemia in patients with CAD, the evidence is inconclusive because of lack of control groups and significant drops in MAP. Furthermore, the isoflurane was administered in above MAC levels or as an induction agent, methods we believe to be different from common clinical usage in patients undergoing CABG surgery. From our preliminary results, there is no evidence that isoflurane is associated with a significantly higher incidence of ischemia than enflurane when these agents are used in moderate doses in conjunction with fentanyl, and their impact on hemodynamic variables is comparable.

TABLE I - INCIDENCE OF ISCHEMIA BY STUDY PERIOD AND AGENT

	P1	P2	P3
ISOFLURANE	2/12	3/12	3/12
ENFLURANE	2/11	1/11	1/11
P Value	NS	NS	NS

TABLE II - HEMODYNAMIC VARIABLES BY STUDY PERIOD AND AGENT

		HR	CO	MAP	SVRI	PCW
P1	I	64±8	4.78±0.6	95±15	2890±550	12±2
	E	64±10	5.10±0.8	90±12	2567±451	11±2
P2	I	53±8	4.07±0.8	82±14	2736±864	11±3
	E	50±7	4.24±0.5	73±9	2371±412	12±2
P3	I	47±5	3.17±0.4	80±8	3466±567	14±3
	E	48±7	3.38±0.9	83±10	3494±830	14±2

All values ± SD
NS between agents

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Title: EFFECT OF EXTREMITY TOURNIQUET DEFLATION ON END-TIDAL pCO_2 VALUES

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Introduction: Since the advent of capnography anesthesiologists are better able to measure and detect the acute variations of end-tidal partial pressure of carbon dioxide ($ETpCO_2$) during various types of surgery. We have recently observed an acute increase in $ETpCO_2$ following the release of an extremity tourniquet during orthopedic surgery. A sudden increase in pCO_2 may have a significant detrimental effect in certain patients, such as head injury patients with an elevated intracranial pressure. These patients frequently undergo orthopedic and other procedures on the extremities with the application of a tourniquet. The purpose of the present study is to investigate the effect of tourniquet release on $ETpCO_2$ measurements in patients undergoing extremity surgery requiring the placement of a tourniquet.

Methods: Twenty-four patients undergoing extremity surgery requiring tourniquet placement were included at random in this study without regard to ASA physical status and divided into two groups. Group A consisted of twelve patients with upper extremity surgery and Group B consisted of twelve patients undergoing lower extremity surgery. All patients received general endotracheal anesthesia. Anesthesia was induced with sodium thiopental (4-5 mg/kg,IV) and endotracheal intubation was performed with the use of succinylcholine (1.5 mg/kg, IV). Anesthesia was maintained with either isoflurane or halothane and nitrous oxide in oxygen. Patient monitoring systems included an EKG, BP, pulse oximetry, esophageal temperature, and end-tidal gas analysis by mass spectrometry (SARAcap AMIT). All patients were ventilated mechanically and $ETpCO_2$ was maintained at approximately 30 mmHg. $ETpCO_2$ values were recorded immediately before tourniquet deflation and 1, 2, 3, 4, and 5 min after tourniquet deflation. Data were analyzed for statistical significance using multifactor analysis of variance and multiple range testing by LSD. In addition, data were analyzed using Friedman two-way analysis of variance by ranks. A p value less than 0.05 was considered statistically significant.

TABLE

End-tidal pCO_2 (ETpCO2) values, immediately before the tourniquet is released (BTR) and 1 - 5 min after the tourniquet is released (ATR).

Time	$ETpCO_2$, mmHg (Mean±SEM) Upper Extremity	 Lower Extremity
BTR	29.70±1.31	31.71±1.08
1 min ATR*	31.63±1.48	37.86±0.96
2 min ATR*	32.50±1.61	40.08±1.02
3 min ATR*	32.27±1.66	40.54±1.06
4 min ATR*	31.86±1.60	39.66±1.01
5 min ATR*	32.13±1.62	38.28±1.01

* Significantly different when compared to BTR ($p<0.05$).

Results: The table shows the mean $ETpCO_2$ values of both groups. The increase in $ETpCO_2$ ranged from 1 to 12 mmHg following the release of the upper extremity tourniquet and from 5 to 18 mmHg following the release of the lower extremity tourniquet. The increase in $ETpCO_2$ was significant at all time intervals after the tourniquet was released when compared to the $ETpCO_2$ value noted before the tourniquet was released ($p<0.05$). There was no correlation between the duration of tourniquet time and rise in $ETpCO_2$ ($p>0.05$).

Discussion: Arterial pCO_2 is a major factor influencing cerebral blood flow and intracranial pressure. Not infrequently, patients with increased intracranial pressure come to the operating room for extremity surgery. This study has demonstrated that there is a significant elevation of pCO_2 following the release of an extremity tourniquet. We believe this pCO_2 elevation may further increase intracranial pressure.

We have not investigated the mechanisms responsible for an increase in pCO_2 following the release of tourniquet in our patients. Possible mechanisms are: (1) During the ischemic period of tourniquet inflation, acid metabolites accumulate which, upon reperfusion of the extremity, are buffered by plasma bicarbonate with a concomitant acute rise in arterial pCO_2 [1]. (2) Anaerobic metabolites produce a temporary state of reactive hyperemia and hypermetabolic state upon recirculation.

Benzon noted increased lactic acid levels 10 min after tourniquet deflation [2]. Haljamae found a 225-300% increase in ischemic muscle lactate content during tourniquet use, with return to baseline levels 5 min after tourniquet deflation [1].

In conclusion, our study demonstrated that there is a significant increase in $ETpCO_2$ levels following the release of an extremity tourniquet. This increase is threefold higher in patients with surgery involving the lower extremity when compared to the upper extremity. We recommend monitoring of $ETpCO_2$ and hyperventilation just before and a few minutes after the tourniquet is released to maintain the desired pCO_2, especially in patients with raised ICP.

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Title: FAMOTIDINE, A NEW H_2 RECEPTOR ANTAGONIST

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Introduction. Pulmonary aspiration of gastric contents is a significant concern to anesthesiologists. Outpatients are recognized to be at increased risk for aspiration pneumonitis due to elevated gastric acidity and volume[1]. The beneficial effects of the H_2 receptor antagonists cimetidine and ranitidine on gastric acidity and volume are well known.[2,3] Famotidine, a new H_2 receptor antagonist, with a duration of action lasting 10-12 hours, has not been evaluated for aspiration pneumonitis prophylaxis. The purpose of this study was to compare famotidine to placebo and ranitidine in an outpatient population when administered as a single dose the night prior to surgery .

Methods. The protocol was approved by the institutional Internal Review Board for Human Research. 45 ASA Class 1&2 outpatients scheduled for elective surgery under general anesthesia were recruited to participate in the study. Patients with preexisting gastrointestinal diseases were excluded. Informed consent was obtained from each patient. Patients were randomly assigned into 3 groups in a double-blinded fashion. Patients in group I were adminstered a placebo to serve as a control. Patients in group II received ranitidine 150 mg, and patients in group III received famotidine 40 mg. Each patient was instructed to take the pill just prior to retiring the night before their scheduled surgery. No other premedications were given.

On arrival in the operating room the patients were questioned as to the time their medication was taken. The time of anesthesia induction was recorded and in each case induction was accomplished with thiopental followed by a muscle relaxant to facilitate tracheal intubation. An 18Fr Salem sump tube was inserted into the stomach and each patient was tilted side to side and placed in 45 degrees Trendelenburg position to facilitate complete recovery of gastric contents. The aspirate was collected in a mucus trap. The volume of the aspirate was measured and the pH was determined immediately with a pH wand (Cole Palmer Model 5985-75). Statistical analysis was calculated using one way analysis of variance. A p value of <0.05 was considered significant. Values are expressed as mean ± SEM.

Results. We were unable to measure pH on one sample in the famotidine group due to inadequate volume. There were no significant differences between groups regarding sex, weight (57 ± 1.4 kg), height (65 ± .5 inches), time interval from pill ingestion until induction of anesthesia (708 ± 18 min). All patients had gynecological or plastic procedures. The results of gastric pH and volume measurements are shown in table 1.

Group	Average Gastric Volume	Average pH	# with Vol ≥ 25	# with pH ≤ 2.5	# with Both
placebo n=15	19.9 ± 3.98	** 2.1 ± .46	6 (37.5%)	13 (86.7%)	5 (33%)
famotidine n=14	18.7 ± 3.97	3.7 ± .58	5 (31.3%)	7 (50%)	2 (13%)
ranitidine n=15	17.9 ± 3.02	** 4.32 ± .56	5 (31.3%)	4 (26%)	3 (20%)

**Gastric pH for ranitidine was significantly different from placebo. However, famotidine was not significantly different from either ranitidine or placebo. Gastric volumes were not significantly different between any groups.

Discussion. Famotidine given as a single dose the night prior to surgery did not reduce gastric pH and volume to provide adequate protection against aspiration pneumonitis. Ranitidine provided significant protection compared to placebo. The lack of effect on gastric volume suggests that the double dose regimine, described by Manchikanti et al[3], which consists of a second dose the morning of surgery is more effective. Our study also supports the belief that outpatients are at risk for aspiration pneumonitis due to increased acidity of gastric contents. We conclude that neither famotidine nor ranitidine provide optimal protection against aspiration pneumonitis when given as a single dose the night prior to surgery and that a double dose regimen should be employed in for aspiration prophylaxis in outpatients.

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Title: PREDICTORS OF POSTOPERATIVE RESPIRATORY FAILURE IN THE PRETERM INFANT AFTER INGUINAL HERNIA REPAIR

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INTRODUCTION. Controversy exists as to the optimum age for inguinal hernia repair in preterm infants. The anesthesiologist's concern regarding postoperative respiratory complications often conflicts with the surgeon's desire to repair the hernia before intestinal obstruction occurs. Pre-existing medical conditions which predict postoperative respiratory dysfunction have been well described for the adult population. In contrast, few investigators have attempted to correlate preoperative illness with postoperative morbidity in premature infants. Comparing postconceptual age (PCA) or prior illness with postoperative complications suggest a PCA of 40 weeks or greater to be an acceptable lower limit provided there is no history of pre-operative apnea or pulmonary disease[1]. We retrospectively examined preoperative factors which correlated with post-operative morbidity for the premature infant undergoing inguinal hernia (IH) repair.

METHODS. After obtaining institutional approval, a retrospective study of all premature infants with previous medical problems undergoing inguinal herniorrhaphy prior to discharge between 1984 and 1987 was performed (N=20). Mean gestational age was 28 weeks (± 3.6) and mean age at operation was 9 weeks (± 3.6). Mean post conceptual age was 38 weeks (± 2.5). Mean operative weight was 2145 grams (± 450). Preoperative illness was defined as any condition requiring active treatment time from birth to date of operation. Weight at birth and operation, gestational and conceptual ages, preoperative medications and disease states (cardiovascular or pulmonary disease, intraventricular hemorrhage, necrotizing enterocolitis, apnea, sepsis, anemia, et cetera) were recorded. All postoperative complications were examined. Apnea, periodic breathing, bradycardia, or the need for mechanical ventilation were tabulated. Data are expressed as a percentage or mean ± standard deviation. Statistical analysis was performed using chi-square, Fischer's exact test, and Student's (unpaired) t-test for independent samples. $P<0.05$ is considered significant.

RESULTS. The overall postoperative complication rate was 60% ($p<0.05$). Infants with a previous diagnosis of respiratory distress syndrome (RDS) had a 90% incidence of at least one postoperative complication ($P=0.004$). This compares with only a 22% complication rate if no previous RDS existed. Gestational age at birth correlated positively with a need for postoperative mechanical ventilation in infants with birth weights less than 2000 grams. There was no statistically significant correlation between postoperative complications and the following ($p=NS$): preoperative apnea and bradycardia, age or weight at operation, or preoperative xanthine therapy.

DISCUSSION. Despite optimal medical management, this study demonstrates a high postoperative complication rate for IH repair performed prior to discharge. A very strong correlation existed between morbidity and previous RDS. These data support the work of Mayhew et al which also point to previous respiratory distress syndrome as a strong predictor of post-operative complications[1]. Prolonged ventilation, apnea or bradycardia, has been previously described in this population[2]. Unlike these reports, preoperative apnea and bradycardia did not predict postoperative respiratory complications in our study.

Whether it is better to precede with early repair or wait is an ongoing debate. Anesthetic risks must be weighed against data which suggests a 31% incarceration rate if repair is postponed[3]. Incidence of incarceration in preterm infants has been estimated to be 5X greater when compared to healthy full-term infants. While most complications were self-limited, this study shows infants with a preoperative history of RDS to be at a nearly 4-fold increased risk for clinically significant postoperative complications. If early surgical repair is necessary, preoperative RDS is an effective marker which can alert the clinician to anticipate postoperative complications and avoid serious sequelae in these high risk infants.

Complication rates in preterm infants (N=20)

Overall:	60%
Prolonged ventilation:	45%
Postoperative apnea:	20%
Postoperative bradycardia:	25%
Other:	25%

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Title: ASA CLOSED CLAIMS STUDY: CAN PULSE OXIMETRY AND CAPNOMETRY PREVENT ANESTHETIC MISHAPS?

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Introduction. In the last decade an explosion of monitoring technology has led to the introduction of new, often expensive, monitoring devices into anesthesia practice, under the assumption that additional monitors should improve patient safety. In fact, no large studies exist that address the validity of this contention.

In 1985 the Professional Liability Committee of the ASA began a nationwide study of closed insurance claims for anesthetic mishaps. Anesthesiologist reviewers were asked, among other things, to evaluate if monitoring techniques available as of 1985 or later could have prevented the complications in each case. The present report presents data obtained from the ASA Closed Claims Study which bears on whether or not additional monitoring could have prevented anesthetic mishaps, and if so, which monitors would have been most useful.

Methods. The ASA Closed Claims Study is an ongoing review of closed claims obtained from 17 professional liability insurance carriers. The cases occurred between 1975 and 1988. The review involved one or more anesthesiologist committee members visiting each insurance company to review claims against anesthesiologists which had been settled or adjudicated. Cases where inadequate information existed either to reconstruct the sequence of events, or to determine cause and nature of the injuries were excluded, as were cases involving dental damage only. All other cases were summarized and reported on standardized data collection instruments.

The data collected included monitors employed, critical incidents, clinical signs present and outcome. The reviewer was required to render a judgement as to whether additional monitoring, even if not available when the case occurred, could have prevented the mishap. Each case was also assigned a "severity of injury" score by the reviewer based on the insurance industries' 10 point scale; where zero indicated no injury; 1-4 indicated temporary injury; 5 indicated permanent but non-disabling injury; 6-8 indicated permanent and disabling injuries; 9 was assigned for death.

There were 15 physician anesthesiologists involved in the onsite reviews, who represented a broad spectrum of clinical experience from both private and academic practice.

Results. To date 1175 closed claims have been reviewed. In 1097 cases sufficient information was available to judge whether additional monitors could have prevented the mishaps. *In 346 (31.5%) of those 1097 cases, the mishap was deemed preventable by additional monitoring.* In 751 cases (68.5%) the application of additional monitors was judged not preventative. Of additional interest was the fact that the mean severity of injury score was 8.3 for complications judged preventable by additional monitoring; whereas, incidents not deemed preventable had a mean severity of injury score of only 5.0. The mean cost of settlement or judgement of cases judged preventable by additional monitoring was $494,000 compared with $170,000 for cases deemed not preventable.

The pulse oximeter and end tidal CO_2 monitors were judged most often to be potentially efficacious. Applied individually, complications and/or death were judged preventable in 138 and 8 cases respectively. If used together, they were judged beneficial in an additional 176 cases. Thus, the reviewers considered that pulse oximetry plus capnometry could have prevented 93% of the mishaps deemed preventable. Other monitors, including PA catheters, were judged potentially effective in preventing complications in only 24 additional cases.

Discussion. Many studies have attempted to determine causes of anesthetic mishaps.[1,2] Some have suggested that additional monitoring might have been preventative.[3,4] To our knowledge, these are the first data which specifically address the potential impact of pulse oximetry, capnometry and other newer devices on anesthetic safety.

The reviewers judged that additional monitoring might have prevented 30% of a large series of complications which resulted in litigation. Most of these preventable incidents involved the respiratory system. Such incidents often lead to devastating results, as is apparent from disparities in severity of injury scores and eventual monetary settlements for injuries judged preventable versus those judged non-preventable with additional monitoring.

We assumed proper application and function of the additional monitors in each case; that the anesthesiologist would have reacted to warnings appropriately; and that the monitors would not themselves have caused additional injuries. Although these assumptions lend a bias favorable to additional monitoring, the fact that these were filed malpractice claims only may reverse the bias, i.e. it might be reasonable to assume that numerous incidents did not result in claims.

It is clear that application of additional monitors - usually pulse oximetry and capnometry, could have prevented a significant number of these anesthesia-related mishaps. This is not necessarily criticism of the anesthetic care rendered in these cases, since most cases occurred before general monitor availability. We conclude that these data do provide solid evidence that pulse oximetry in combination with capnometry can be expected to aid substantially in prevention of anesthetic-related morbidity and mortality.

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Title: UPTAKE OF ISOFLURANE IN ELDERLY PATIENTS

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Introduction. The uptake of volatile anesthetic agents has been studied in young healthy adults by measuring the rise of end-tidal (alveolar) concentrations(1). There is little information, however, on the effects of the physiological changes of ageing on uptake. This study compares the rise of end-tidal concentrations of isoflurane in young and elderly patients at induction of anesthesia.

Method. Twenty-four patients graded ASA I or II presenting for elective orthopedic procedures were studied prior to surgery; 12 were aged between 18 and 35 yr, 12 were 60 yr or over. Patients taking cardioactive drugs were excluded. Informed consent was obtained and approval was given by the University Medical Research Ethical Committee.

Patients were anesthetised with a sleep dose of thiopental, pancuronium 0.1 mg/kg and alfentanil 15μ g/kg. After manual ventilation with 100% O_2 in an open circuit, the trachea was intubated. Intermittent positive pressure ventilation continued with 100% O_2 and was adjusted to maintain a constant end-tidal CO_2 concentration of 35 mmHg. Isoflurane (1%) was added and the inspired (F_i) and end-tidal (F_e) isoflurane concentrations were measured continuously for 20 minutes using a Datex Normac CD300 infra red vapor analyser. Isoflurane concentrations were recorded on a Hewlett Packard 7754B four-channel writer with the cardiovascular and respiratory measurements. The ratio F_e/F_i was used as an index of uptake.

Data were analysed using the Mann Whitney U test and a P value of < 0.05 was considered significant.

Results. The groups were similar in terms of weight and sex distribution; mean ages (yr) (SD) were 25.9 (5.2) and 68.7 (7.1).

Table 1. Mean (SD) end-tidal (F_e) to inspired (F_i) isoflurane ratios.

Time (min)	F_e/F_i young	F_e/F_i elderly
1	0.345 (0.038)	0.398 (0.044)*
2	0.398 (0.031)	0.444 (0.039)*
3	0.445 (0.026)	0.464 (0.031)
4	0.477 (0.035)	0.480 (0.030)
5	0.511 (0.032)	0.509 (0.027)
7	0.552 (0.037)	0.537 (0.037)
10	0.598 (0.028)	0.569 (0.039)
12	0.621 (0.031)	0.588 (0.045)
15	0.650 (0.032)	0.603 (0.043)*
17	0.658 (0.031)	0.611 (0.044)*
20	0.675 (0.031)	0.619 (0.051)*

*$P < 0.05$

Greater cardiovascular depression occurred in the elderly patients.

The mean F_e/F_i ratios rose rapidly initially in both groups (Table 1).

After the first 2 minutes of anesthesia, F_e/F_i rose more slowly in the elderly group and after 15 minutes of anesthesia, it was significantly lower than in the young. Values in the young patients were comparable to those found previously in young volunteers(2).

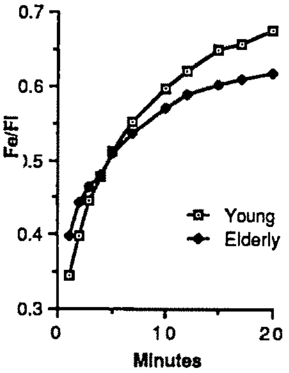

Figure 1. End-tidal concentrations of isoflurane in young and elderly patients at induction of anesthesia.

Discussion. The rise of end-tidal concentration of isoflurane at induction of anesthesia was slower in elderly than in young patients, suggesting that induction of anesthesia using a given concentration of isoflurane takes longer in the elderly.

This finding is surprising in view of the increased cardiovascular depression that occurred in the elderly patients and the lower blood gas solubility of isoflurane in old age(3).

It may be explained by the increased tissue solubility of isoflurane in old age(4), and the respiratory changes which occur with ageing, including increased functional residual capacity(5).

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Title: HUMAN MUSCLE SYMPATHETIC EFFERENT NERVE ACTIVITY IS AUGMENTED BY NITROUS OXIDE.

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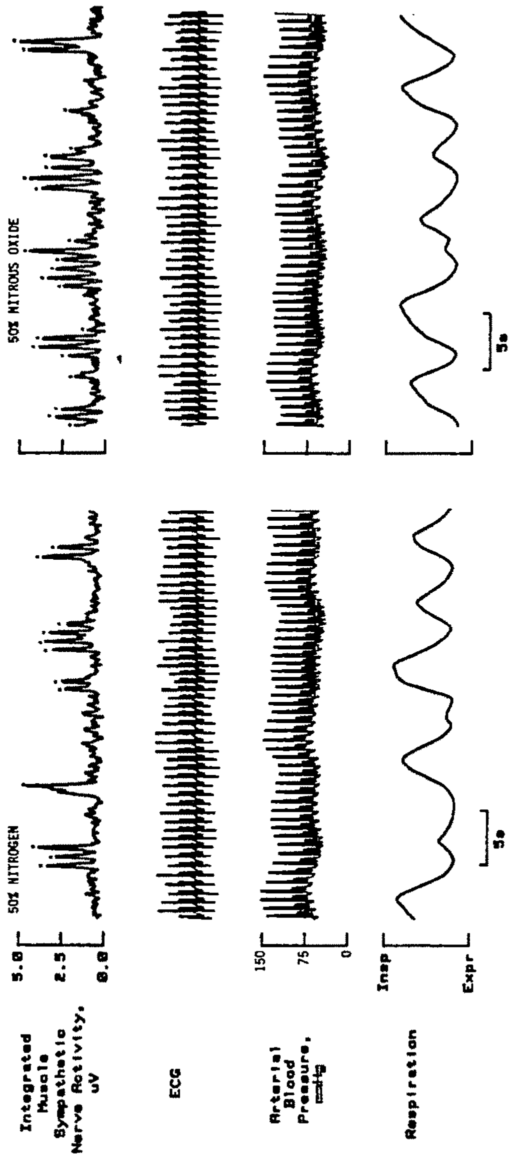
Introduction. Nitrous oxide (N_2O) is thought to activate the sympathetic nervous system. Previous work has demonstrated that plasma norepinephrine levels and peripheral resistance increase and the pupils dilate during administration of N_2O to healthy volunteers (1). In the present study, we provide the first direct evidence of postganglionic muscle sympathetic efferent nerve activation by N_2O in healthy volunteers.

Methods. After approval by the Institution's Human Research Review Committees, 3 healthy young (20, 22, 27 yrs) volunteers consented to be studied. Subjects were instrumented with a radial artery catheter for determination of systolic and diastolic blood pressure (SP, DP), a jugular vein catheter to detect central venous pressure (CVP) ECG and impedance electrodes to determine stroke volume (SV) and derive cardiac output (CO) and total peripheral resistance (TPR). A mass spectrometer was used to monitor end-tidal CO_2 and N_2O concentrations. Muscle sympathetic nerve activity (MSNA) was detected from a percutaneous needle microelectrode inserted into a muscle nerve fascicle within the peroneal nerve just distal to the knee and below the head of the fibula. Characteristic muscle sympathetic integrated bursts of activity were sought by fine manipulations of the needle until a site was obtained with spontaneous bursts of activity. Bursts were noted to be pulse-synchronous and to increase in frequency during phase 2 and 3 of Valsalva's maneuver. Once an acceptable site was obtained, subjects remained relatively immobile (but confortable) throughout the study. A face mask was placed and subjects breathed oxygen mixed with 50% nitrogen for 20 min followed by 2 consecutive 10 min periods of breathing 25% and 50% N_2O in oxygen. Data were averaged from the last 6 min of each period.

Results. Average baseline HR (50+3 bpm) was unchanged during 25% N_2O and increased 5 bpm during 50% N_2O. End-tidal CO_2, SV, CO, TPR and SP were unchanged throughout each study period, however, DP increased significantly by 2 and 4 mmHg during 25% and 50% N_2O respectively. Additionally, CVP increased by 0.5 and 1.0 mmHg during N_2O periods. Baseline MSNA (19.8 bursts/100 heart beats) increased significantly by 54% and 52% during 25% and 50% N_2O breathing. A recording from one subject is shown in the figure. Integrated bursts of MSNA are identified by a small dot above each burst. There were 12 bursts identified in the 30 sec of data while breathing 50% O_2: 50% N_2. When breathing 50% N_2O, there were 22 bursts recorded (note that respiratory reductions of DP commonly elicit bursts of MSNA).

Discussion. The present data provide the first direct evidence that brief exposure to N_2O elicits significant augmentations of sympathetic outflow in young volunteers. This response may provoke the small but significant increases in DP and CVP.



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TITLE: HEMODYNAMIC IMPACT OF ESMOLOL DURING NITROPRUSSIDE-INDUCED HYPOTENSION.

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Introduction: Esmolol is known to markedly decrease sodium nitroprusside (SNP) dose-requirement for producing deliberate intraoperative hypotension.[1] This effect is associated with reductions in heart rate, plasma renin activity and catecholamine levels. Esmolol also has been shown to reduce cardiac output in patients undergoing cardiovascular surgery,[2] but the hemodynamic impact of Esmolol during SNP-induced afterload reduction is, as yet, unknown. Because Esmolol appears to be an ideal agent both for potentiating SNP and for preventing rebound hypertension, the following study was initiated to further elucidate its mechanisms of action during controlled hypotension in man.

Methods: The subjects of this investigation were 6 adult male patients, ASA physical status I and II, scheduled for major operative procedures utilizing controlled hypotension. The protocol was approved by our Institutional Review Board, and informed consent was obtained on the night before surgery.

A thermistor-tipped Swan-Ganz catheter and radial artery cannula were placed and the following measurements were made: heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and cardiac output by thermodilution technique. The following derived parameters were calculated from appropriate formulae: Cardiac Index (CI), stroke volume (SV), Systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR).

General anesthesia was induced with thiopental, 3 mg/kg, and a loading dose of Fentanyl, 5μg/kg. Anesthesia was maintained with an infusion of Fentanyl, 8-10 μgs/kg/hr, 60% N_2O in O_2 and pancuronium, 0.1 mg/kg. Ventilation was controlled to maintain a $PetCO_2$ of 30-35 mm Hg.

Hemodynamic parameters were collected at the following times: 1) Prior to induction of anesthesia, 2) During stable anesthesia at normotension, 3) During SNP-induced hypotension (MAP=56 mm Hg ± 2 SE), 4) After 20 minutes of esmolol infusion at 200, 300 and 400 μg/kg/min, respectively, with SNP reduced to maintain MAP at the same level of hypotension, 5) 20 min after SNP and Esmolol were terminated, and 6) on arrival in the PACU.

Statistical comparisons were performed using Analysis of Variance for repeated measures; $P < .05$ was regarded as significant.

Results: Our results are summarized in the table. As expected, SNP-induced hypotension was associated with significant reductions in SV, RAP and PCWP. Esmolol infusion markedly lowered the dose-requirement for SNP and had profound hemodynamic effects, with significant reductions in HR and CI and significant increases in RAP and PCWP as compared to values obtained during SNP-induced hypotension alone. There was no evidence of rebound hypertension after discontinuation of the Esmolol and SNP infusions; hemodynamic data obtained in the recovery room were no different from awake control values.

TABLE

	NORMO-TENSION	ESMOLOL =0	ESMOLOL =200	ESMOLOL =300	ESMOLOL =400
SNP DOSE (μg/kg/min)	0	5.6 ± 1.0	$.5 \pm .8$	$1.6 \pm .3^{+}$	$0.8 \pm .3^{+}$
HR(bpm)	86 ± 5	99 ± 5	$74 \pm 6^{+}$	$69 \pm 5^{+}$	$67 \pm 4^{+}$
MAP(mmHg)	84 ± 7	$56 \pm 3^{*}$	$56 \pm 3^{*}$	$57 \pm 2^{*}$	$57 \pm 3^{*}$
RAP(mmHg)	9 ± 1	$5 \pm 1^{*}$	$7 \pm 1^{+}$	$10 \pm 1^{+}$	$11 \pm 2^{+}$
PCWP(mmHg)	9 ± 1	$5 \pm 1^{*}$	$7 \pm 1^{*}$	$10 \pm 1^{+}$	$10 \pm 2^{+}$
CI ($l/min/m^2$)	$5.2 \pm .3$	$4.6 \pm .4$	$3.4 \pm .4^{+}$	$3.1 \pm .6^{+}$	$2.7 \pm .6^{+}$
SV (ml)	119 ± 12	$94 \pm 11^{*}$	$88 \pm 7^{*}$	$85 \pm 12^{*}$	$76 \pm 14^{*}$
SVR (dyne. sec.cm^{-5})	624 ± 80	479 ± 57	643 ± 80	770 ± 171	913 ± 236

All values: Mean ± SE
* = P<.05 vs Normotension values.
+ = P<.05 vs 0 Esmolol dose.

Discussion/Conclusion: These data indicate that Esmolol has a profound impact on cardiac performance during SNP-induced intraoperative hypotension. This is primarily a function of decreased CI induced by the marked reduction in HR. The decrease in CI is accompanied by a significant increase in preload, suggesting an effect of Esmolol on myocardial contractility. This is also suggested by the trend toward decreasing SV and increasing SVR with increasing Esmolol infusion rates, although these changes did not achieve statistical significance.

We conclude, then, that potentiation of SNP induced hypotension by Esmolol is not only mediated through reduction in plasma renin activity and decreased catecholamine levels, but also occurs because of the marked reduction in cardiac output caused by cardioselective beta blockade.

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Title: DO SPINAL ENKEPHALINS MEDIATE ANALGESIA DURING PREGNANCY?

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Introduction. Endogenous spinal opioid system activation may increase pain threshold during pregnancy (1) and following a painful stress (2). Variation in spinal opioid activity is also postulated to explain the large variability in postoperative narcotic analgesic requirements (3). In this study we sought to determine if spinal opioid activity, as measured by CSF enkephalin concentrations, is increased during pregnancy or during painful labor, and whether the level of this activity would predict the amount of narcotic required for postoperative analgesia.

Methods. The Clinical Research Practices Committee approved the protocol. Following informed consent, 45 ASA I or II women receiving spinal anesthesia for elective gynecologic surgery or cesarean section (either elective or following at least 4 hours of painful labor) were studied. Two ml of CSF were obtained prior to injecting spinal local anesthetic and analyzed for free enkephalins and proenkephalins (ProEnks) using specific RIA's. Postoperative analgesia was provided using patient controlled analgesia (PCA) with morphine. Patient age, height, weight, and level of pain (10 point verbal scale) before and 24 hours following surgery were recorded. Data were analyzed using mean, median, SEM, one-way analysis of variance, linear regression, and Student's t-test with Bonferroni correction. $P < 0.05$ was considered significant.

Results. The groups did not differ in height or weight, but did in age (nonpregnant = 35 ± 2 years, elective cesarean = 29 ± 1 years, labor cesarean = 25 ± 1 years; all groups differ). Only the labor/cesarean section group had preoperative pain (median pain score = 7), and 3 of these patient had received preoperative narcotics (1 mg butorphanol in 2, 5 mg morphine in 1). Postoperative pain scores were similar in all groups. CSF free enkephalins were not detectable in any group. However, the labor cesarean section group had numerically greater CSF ProEnks ($P = .07$) and significantly decreased PCA morphine use (Table 1). Although individual CSF ProEnks and postoperative narcotic use were unrelated, there was a significant correlation between these variables among the 3 group means (Fig. 1).

Discussion. 1) The increase in pain threshold observed during pregnancy is reversible with intrathecal naloxone, suggesting a spinal opiate mechanism. Of the 3 opioid peptide families (β-endorphin, dynorphin, and enkephalin), only enkephalin precursors are reported to be increased in CSF during pregnancy (1). Our data do not substantiate this preliminary report, perhaps due to differences in control groups (older patients scheduled for surgery in our study vs young, healthy volunteers). 2) Stress-induced analgesia occurs in animals in part by an opiate mechanism. Although alternative explanations are possible, our data in patients following painful labor are consistent with a similar phenomenon in humans. 3) Our data also suggest that CSF ProEnks concentrations may partially explain the variation in postoperative analgesic requirements among these groups of patients.

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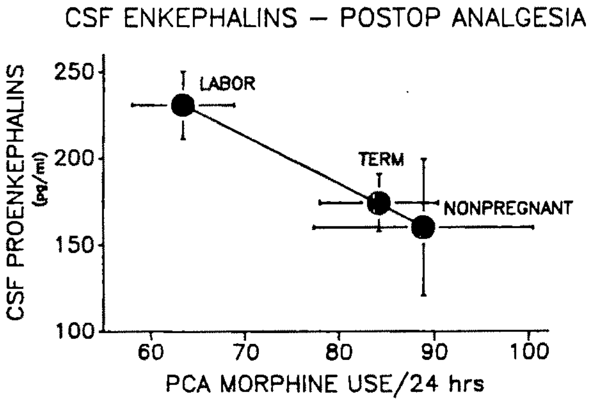
TABLE 1: CSF PROENKS AND NARCOTIC USE

Group	N	ProEnks (pg/ml)	PCA Morphine (mg/24 hr)
Nonpregnant	11	162 ± 25	90 ± 11
Elective C/S	21	174 ± 16	84 ± 6
Laboring C/S	13	223 ± 16	63 ± 5*

* P < .01 vs other groups

FIGURE 1:



Title: EPIDURAL CLONIDINE ANALGESIA: AN OPEN-LABEL, DOSE-RANGING STUDY

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Introduction. Animal studies suggest that activation of spinal α2-adrenoceptors by clonidine produces profound analgesia (1). Preclinical toxicity testing of epidural clonidine is reasonably complete, and anecdotal reports suggest that epidural clonidine, 100-300 μg, effectively treats postoperative pain in humans (2). We report our experience on the safety and efficacy of epidural clonidine, 100-700 μg, for postoperative analgesia.

Methods. The Clinical Research Practices Committee approved the protocol, and clonidine was supplied under an IND from the FDA. Eighteen ASA I, II, or III patients undergoing upper abdominal surgery or total knee arthroplasty (TKA) were studied. An epidural catheter was inserted and tested preoperatively, following which the patient received either general or epidural anesthesia for the surgical procedure. In the recovery room, when the patient first requested pain medication, 3 ml of 1.5% lidocaine with 15 μg epinephrine were injected epidurally, followed in 5 min by clonidine, diluted in 10 ml saline. In this dose escalation study, 3 patients were studied at each clonidine dose (100-700 μg in 100 μg increments). Some TKA patients received 2 clonidine doses, separated by 24 hours. Supplemental analgesia was provided by patient controlled analgesia (PCA) with iv morphine. We recorded patient demographic data and obtained blood for arterial blood gas tension, clonidine, cortisol, and glucose analysis before and 1 hour after injection. We also monitored morphine use, pain and sedation (4 point verbal scales), neurological function, and blood pressure and heart rate at intervals for 6 hours following epidural injection. Only descriptive statistics (mean, SEM) were performed.

Results. Pain scores decreased 20 min following injection (all doses), but this effect was short-lived with doses of < 400 μg (Table 1). Blood pressure and heart rate decreased following clonidine injection (Fig. 1). The maximal blood pressure decrease following clonidine occurred 20-60 min following injection, and 5 patients received ephedrine for a > 30% decrease in blood pressure. Clonidine did not alter arterial blood gas tensions (Po2 was 110 ± 6 mmHg before, 94 ± 8 mmHg after) or serum glucose (124 ± 12 mg/dl before, 131 ± 10 mg/dl after). In 10 of the patients cortisol decreased following injection. This decrease (-40 ± 8%) was not dose-dependent. Clonidine produced moderate, transient sedation, which was not dose-dependent. Serum clonidine 1 hour following epidural injection ranged from 224 pg/ml following 100 μg to 1918 pg/ml following 700μg.

Discussion. Based on its lipid solubility, clonidine should have an onset and duration of action of analgesia resembling epidural fentanyl. Our data support this hypothesis, and do not substantiate previous reports of prolonged analgesia following bolus epidural clonidine injection (2). Unlike results in sheep (1), epidural clonidine does not alter serum glucose or arterial Po2, but does decrease blood pressure in humans. Compared to oral administration, epidural clonidine injection produces similar serum clonidine concentrations, and likewise produces similar effects on blood pressure, heart rate, and stress-induced cortisol secretion. Hemodynamic depression and short-lasting analgesia may limit the usefulness of bolus epidural clonidine analgesia in the postoperative setting. Supported in part by FD-R-00171 from the FDA and a grant from LyphoMed, Inc.

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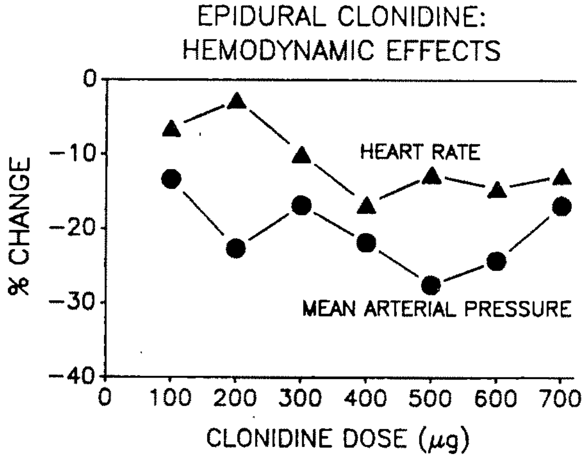
TABLE 1: DURATION OF EPIDURAL CLONIDINE ANALGESIA

Clonidine Dose	Time to First PCA Morphine(hr)	Time to 10 mg. Morphine (hr)
100 μg	1.2	2.7
200 μg	1.1	2.3
300 μg	0.5	2.0
400 μg	2.3	4.7
500 μg	3.3	5.5
600 μg	2.5	7.2
700 μg	3.2	4.7

FIGURE 1: HEMODYNAMIC EFFECTS 1 HOUR AFTER INJECTION



Title: SENSITIVITY TO VECURONIUM IN MYASTHENIA GRAVIS: A DOSE-RESPONSE STUDY

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Introduction. Patients with myasthenia gravis (MG) are known to be sensitive to the neuromuscular blocking effects of non-depolarizing muscle relaxants yet few reports have quantified this sensitivity(1). The purpose of the present study was to use a cumulative dose plus infusion (CDI) technique (2) to establish dose-effect relationships for vecuronium (VEC) in patients with and without MG.

Methods. Twenty normal and 10 MG patients gave their written informed consent to participate in this institutionally approved study. The normal patients were ASA physical status 1, free from medications or conditions known to affect neuromuscular transmission, and scheduled to undergo gynecologic or orthopedic procedures. The MG patients were ASA PS 2 or 3, Osserman Class IIB-IV (3), and scheduled to undergo thymectomy as a treatment for their MG. All MG patients were receiving pyridostigmine (PYR) but only 4/10 received it on the morning of surgery. Three of the 10 were receiving steroid therapy, also given preoperatively. In all cases of MG the diagnosis had been confirmed by EMG testing. All patients were premedicated with diazepam 5-10 mg P.O. Anesthesia was induced with thiamylal and maintained with N_2O and incremental doses of fentanyl. Potent inhaled agents were avoided. Ventilation was controlled with bag and mask to maintain end-tidal CO_2 within the normal range. Train-of-four (TOF) stimulation was applied to the ulnar nerve at the wrist every 10s and the integrated EMG responses of the first dorsal interosseous muscle were recorded using a Datex 221 neuromuscular transmission monitor (Puritan-Bennett). After stabilization of the response patients received VEC (5 or 10mcg/kg) followed by similar incremental doses with an infusion of VEC, the rate of which was adjusted to replace eliminated drug (2). Incremental doses were administered and the infusion rate increased, when three consecutive equal first responses (T1) were observed in the continuously monitored EMG TOF, until a 95-99% T1 decrement was achieved. Linear regressions were obtained between the logit transformation of neuromuscular blockade and the log of the cumulative VEC dose. A regression line was calculated for each patient, from which the ED50 and ED95 were derived. Means of these values were obtained for the 10 MG and 20 normal patients, and compared using a Student's test for unpaired data. Results are expressed as means with 95% confidence intervals. A p value of less than 0.05 was considered significant.

Results. No complications were associated with the administration of VEC in either group. The mean dose-response curve for MG was shifted to the left but there was no significant difference between the slopes (Figure). The ED values are shown in the Table. The differences between the MG and normal patients in these mean values were highly significant (p less than 0.0001). Those MG patients who received PYR and/or steroids were slightly (but not significantly) less sensitive to VEC than those MG patients who did not.

Discussion. Our results confirm that MG patients are more sensitive to VEC and show that the ED50 and ED95 are 53% and 56% of normal, respectively. Previous reports of the ED80-ED98 for VEC in MG have ranged from 11-80 mcg/kg (4), with one report of ED90 being 19mcg/kg (5). Differences among these and our ED values are likely due to the smaller numbers of MG patients ($n \leq 6$) in previous studies and variety of methods for assessing blockade.

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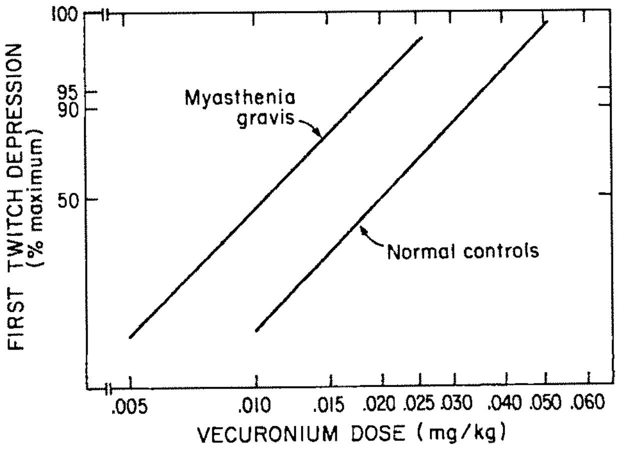
Table

	Normals	Myasthenics
	n=20	n=10
ED50 mcg/kg	18.9*	10.0*
(95% confidence limits)	18.0-19.8	9.8-10.1
ED95 mcg/kg	36.3*	20.2*
(95% confidence limits)	34.6-38.1	17.7-23.1

*$p < 0.0001$



Title: PULMCNARY ARTERY OCCLUSION PRESSURE DOES NOT ACCURATELY REFLECT LEFT ATRIAL PRESSURE AFTER CARIOPULMONARY BYPASS

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The measurement of left ventricular preload is essential in constructing Frank-Starling curves of myocardial performance to guide rational use of inotropes, vasodilators and pressors. Pulmonary artery occlusion pressure (PAOP) has been considered a reliable approximation, and has correlated well with LAP (mean left atrial pressure) in the cardiac surgical patient post-cardiopulmonary bypass (CPB) and post-operatively.[1] Although left ventricular end-diastolic volume (LVEDV) is a truer approximation of myocardial fiber length, and recent work has reported better estimations by radio nucleotide scintigraphy and transesophageal 2-D echocardiography, most institutions have only pressure measurements available in the acute clinical setting. PAOP is subject to many variables, and when PAOP and LAP are compared perioperatively there are marked discrepancies beginning several hours post-CPB.[2] Our study aims to examine how PAOP and LAP correlate immediately post-CPB and post-operatively and determine any relationship to PVR, arterial PCO_2 and core temperature. Following institutional human research review committee approval, twenty patients undergoing elective myocardial revascularization with ejection fractions of >0.4 were studied prospectively. PA and LA catheters were placed without regard to this study. Anesthetic management was standardized to a narcotic/benzodiazepine/muscle relaxant/oxygen technique, and surgical management was standardized with left ventricular venting, cooling to 30 C, maintainence of the hematocrit 23-27% during CPB, and intermittent ischemic arrest. PA catheters were placed immediately preoperatively via the right internal jugular vein into the proximal right middle or lower pulmonary artery and LA catheters prior to CPB. No patients required inotropic support or had perioperative infarction or congestive failure, and all patients required sodium nitroprusside post-operatively for 12-24 hours for blood pressure control.

Pressure measurements were made with the same equisensitive transducers intraoperatively as post-operatively (Deseret Model 38-9667) with zero reference point the mid axillary line. Cardiac output and PAOP were measured with a thermodilution pulmonary artery catheter (American Edwards 7.5F model 93A-831) at end expiration. (5cm H_2O positive end expiratory pressure). Temperatures were taken from the PA catheter thermistor in C. Measurements were taken pre-CPB, at fifteen and thirty minutes post-CPB, and at four and eight hours post-op.

Analysis of variance and the least significant difference test were used to test differences between mean PAOP and LAP and to test for changes in mean responses to PAOP, LAP, PVR, pCO_2 and temperature over the five time points. Linear regression analysis was used to test for a relationship of PVR, pCO_2 or temperature to the PAOP-LAP difference.

RESULTS

PAOP and LAP were significantly different pre-CPB,and at 15 minutes post-CPB and 30 minutes post-CPB, but were not statistically different at four and eight hours postop. Though PAOP was lower at four and eight hours post-op than at 30 minutes post-CPB, LAP did not change throughout the study periods. When linear regression and correlation analysis were used the PAOP-LAP difference was not related to PVR (pooled r = -0.07), pCO_2 (pooled r = -0.18) or temperature (pooled r = -0.12).

DISCUSSION

Current explanations for differences in PAOP and LAP measurements after CPB are related to pulmonary venoconstriction from increased interstitial water and differential right and left heart dynamics. We demonstrate significant overestimations of left heart filling by PAOP as compared to the LAP only immediately after CPB that do not extend into the postoperative eight hours. These changes are not related to pulmonary vascular resistance or potential influences on PVR--pCO_2 and temperature. Using PAOP only to guide left ventricular filling in this period may lead to overestimations and therefore misleading Starling curve relationships.

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	Pre-CPB	Post p CPB			
		15 min.	30 min.	4 Hours	8 Hour
PAOP	12.1*	12.4*	14.8*	11.5	11.1
	5.0	3.1	5.9	4.4	3.4
LAP	7.6	8.9	9.2	9.7	9.6
	4.9	2.7	2.6	3.6	3.2
PVR	121.8	135.1	153.8	145.9	143.9
	70.8	70.0	68.9	66.3	69.8
CO_2	34.5	34.6	35.0	39.6	39.9
	2.4	3.8	3.4	2.6	1.8
TEMP	35.9	37.0	36.6	36.4	37.1
	0.4	0.7	0.5	0.9	0.3

Results are shown as mean standard deviation
*Significantly different than LAP mean (P<.01)

Title: PULMONARY ARTERY MEASUREMENTS DURING UNILATERAL LUNG INJURY IN SHEEP

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Introduction. Pulmonary artery (PA) catheters continue to be used despite numerous publications questioning their usefulness (1,2). Patients in the intensive care unit with unilateral lung disease often require use of this catheter. To date, no study has verified the accuracy of the data collected by this monitor in this clinical situation (3). It would seem logical to question the accuracy, because the PA catheter samples blood and pressures in only one pulmonary vascular bed. For this reason, a unilateral lung injury model in sheep was created for simultaneous sampling from both pulmonary vascular beds.

Methods. This study was approved by the institutional animal care committee. Three adult sheep (20-23 kg) were anesthetized with intravenously administered thiamylal and were paralyzed (pancuronium, 0.1 mg/kg). The animals were placed in the supine position, and tracheostomy tubes were inserted. A 41F left double-lumen tube was placed, and its position was confirmed by clinical examination and fluoroscopy (Phillips B.V. 20S C-arm fluoroscope), so that both lung fields were isolated. The animals were mechanically ventilated (Emerson volume ventilator) to maintain PaO_2 and $PaCO_2$ within normal ranges. A PA catheter was placed by coronary guide wire and fluoroscopy into each lung field. Baseline measurements were obtained: static elastic recoil pressure (SERP), arterial blood gases, mixed venous blood gases, core temperature, cardiac output (American Edwards), PA pressures, PA occlusion pressure (PAOP), mean arterial pressure (MAP), and heart rate (Grass model 7D polygraph recorder balanced and calibrated to mercury). At time zero, 2.5 ml of 0.1 N hydrochloric acid was instilled into a mainstem bronchus through the double-lumen tube (two right and one left lung preparations). Simultaneous measurements were made from each catheter at 0, 15, 30, 60, and 90 min. The animals were then sacrificed, and autopsies were done to confirm the placement of the endobronchial tube and the selective placement of each PA catheter in the right or left PA branch. Because of the technical difficulty of the experiment, 12 animals were entered into the study but only 3 experiments were completed successfully.

Results (Table 1). During the experiment, the injured lung had a marked reduction in compliance and an increase in SERP. The non-acid-exposed lung remained stable. PaO_2 decreased, whereas $PaCO_2$ and arterial pH remained stable. QS/QT did not change during the experiment, and results from both catheters remained in close agreement. $(A\text{-}VO_2)d$ increased steadily throughout the study, with values from both catheters changing together. Absolute values were nearly equivalent. Cardiac output measurements decreased linearly in both lung fields to similar degrees. Pulmonary and systemic vascular resistances (PVR and SVR) and PAOPs also were similar between lungs at the same measurement times.

Discussion. Hemodynamic and respiratory measurements obtained with a PA catheter are accurate in unilateral lung injury whether the catheter is located ipsilateral or contralateral to the injury. In this study, the absolute values obtained from each catheter were too few for extensive statistical analysis. The small differences in values in each paired measurement may have been influenced by the method of guidance in placement: coronary wire rather than flow.

References.

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TABLE 1.--Cardiopulmonary Measurements*

	SERP at 10 ml/kg/ lung, cm H_2O		PA pressures, mm Hg		
			Systolic		Diastolic
Min	I	U	I	U	I
0	20.0±9.1	12.0±2.2	30.3±0.5	31.0±5.4	12.3±4.5
15	50.0±5.9	16.3±3.3	41.7±3.3	40.3±8.5	24.7±8.2
30	34.0±9.8	15.6±1.9	36.7±4.5	36.7±7.9	23.3±5.4
60	39.6±4.6	13.6±2.9	38.0±6.4	41.3±10.0	18.7±3.4
90	49.3±6.8	18.0±3.6	37.0±6.5	37.7±7.9	19.0±4.6

	PAP (cont) Diastolic	PAOP, mm Hg		Cardiac output, L/min	
Min	U	I	U	I	U
0	19.7±1.0	0.3±2.5	4.3±2.5	2.14±0.80	2.27±0.48
15	23.7±5.3	12.0±8.6	7.0±5.1	2.14±0.47	2.13±0.34
30	24.3±6.9	6.0±2.2	4.6±0.5	2.34±0.65	1.90±0.45
60	24.7±7.4	7.7±2.6	3.3±0.4	1.81±0.43	1.69±0.36
90	22.0±5.0	7.3±1.7	5.6±2.4	1.47±0.07	1.65±0.26

Min	pH	Pa_{O_2}	Pa_{CO_2}	Base excess, meq/L
0	7.44±0.07	123.7±41.1	40.2±4.1	3.0±5.0
15	7.46±0.05	85.9±22.3	39.0±9.9	3.1±2.1
30	7.42±0.08	96.3±37.7	38.1±10.0	0.3±1.0
60	7.40±0.11	88.1±37.2	41.6±15.9	0.4±1.1
90	7.40±0.12	79.8±30.8	37.3±9.2	-1.5±2.1

	QS/QT		$(A\text{-}VO_2)d$		Heart rate,
Min	I	U	I	U	bpm
0	0.3±0.1	0.2±0.1	2.5±0.5	2.5±0.4	117.3±6.0
15	0.3±0.1	0.3±0.1	3.4±0.5	3.0±0.4	105.0±4.9
30	0.2±0.0	0.2±0.1	3.8±0.6	3.9±0.5	102.3±2.1
60	0.3±0.1	0.3±0.2	4.4±0.2	4.4±0.2	101.0±7.5
90	0.2±0.1	0.2±0.1	5.2±1.0	5.3±1.2	98.7±15.1

	MAP,	SVR		PVR	
Min	mm Hg	I	U	I	U
0	107.5±23.7	4250±806	3738±500	729±197	701±202
15	97.1±4.4	3262±726	3620±615	631±187	916±426
30	99.7±7.1	3761±1568	4419±1482	874±463	1027±200
60	87.8±8.3	4107±1377	4242±960	893±543	1329±515
90	76.3±27.8	3973±1427	3676±1584	957±207	978±49

I, injured lung; U, uninjured lung.

*All values are means ± standard deviations.

Title: PREMEDICATION IN CHILDREN: A COMPARISON OF ORAL TRANSMUCOSAL FENTANYL CITRATE (FENTANYL LOLLIPOP) VERSUS PLACEBO

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Introduction. There is little doubt that surgery can be an emotionally trying experience for pediatric patients. Effective premedication can reduce the incidence of psychological disturbances and provide for a smoother, calmer safer anesthetic course. While initial studies have suggested that oral transmucosal fentanyl citrate (OTFC) in a dose of 15-20 mcg/kg may be a safe and effective premedicant in children and adults, this has not been demonstrated in a randomized double blind fashion.[1,2] The purpose of this study was to determine in a randomized, double-blind manner, the efficacy of a lollipop containing fentanyl citrate as a premedication before surgery in children.

Methods. The study was approved by the Institutional Review Board and written informed consent was obtained from the child's parents or legal guardians. 40 healthy patients, ASA I-II, aged 3-12 yrs (mean 86 months) were divided into 2 groups as follows: Group 1 = placebo lollipop premedication (n=20), Group 2 = fentanyl lollipop premedication (n=20). In a double-blinded fashion, patients were assigned to receive lollipop containing either fentanyl citrate or no active drugs 60-90 min prior to surgery. An appropriately sized lollipop was chosen so that if the patient received fentanyl, the total dose would be 15-20 mcg/kg body weight. Respiratory rate and oxygen saturation (using a Nellcor N100 Pulse Oximeter) were followed until induction of anesthesia. Activity and anxiety scores were assessed at 10 min intervals, according to the following scale. Activity score: 1) asleep; 2) asleep, slowly responds to verbal commands; 3) drowsy, readily responds to verbal commands; 4) awake, calm; 5) awake and active. Anxiety Score: 1) none; 2) little; 3) moderate; 4. excessive. Separation scores were assigned as follows: 1) excellent; patient unafraid, cooperative 2) good; slight fear and/or crying, 3) poor; fear and crying. Induction of anesthesia was accomplished by mask using halothane and 70% nitrous oxide in oxygen. The patients were intubated, and ventilation was controlled during the surgery to maintain E_T CO_2 35–40 mm Hg. The time intervals from induction of anesthesia to extubation and from Post Anesthesia Care Unit (PACU) admission to PACU discharge were noted. Patients were scored upon PACU arrival and discharged according to the following scale: 1) awake, 2) drowsy, 3) barely arousable, 4) asleep. The need for postoperative narcotics for pain control was recorded. Patients were also evaluated for complications. Data were analyzed for statistical significance using Chi square analysis, and paired t-test with $p < .05$ regarded as significant.

Results. There were no significant differences between the two groups with respect to age, weight, duration of anesthesia, and length of stay in the PACU. All children willingly accepted the lollipop. Oxygen saturation and respiratory rates were similar in the 2 groups at baseline. Respiratory rates were significantly lower in the active group at all evaluations after 20 minutes and exhibited a significant decrease over time. Lowest respiratory rates were significantly lower in the active group. There were no significant decreases in oxygen saturation in either group. Oral transmucosal fentanyl citrate (OTFC) produced significantly more sedation at 30 minutes and less anxiety at 20 and 30 minutes as compared to the placebo group. Induction scores were significantly better in the OTFC as compared to the placebo group while the difference in separation scores only approached statistical significance (Table 1). OTFC did not significantly prolong length of stay in the PACU and there was no significant difference in sedation scores between the two groups at the time of discharge. Other side effects occurring infrequently in the active group were bigeminy (2 patients), and bronchospasm, sleepiness, double vision, and premature ventricular contractions (1 patient each). In the placebo group, there was nausea (2 patients), salivation (1 patient), sleepiness (1 patient). Overall, incidence of adverse effects were significantly greater in the active group. Significantly fewer patients who received the OTFC premedication required post-operative narcotics for pain control.

Discussion. We investigated the use of OTFC administered in the form of a pleasant-tasting lollipop as a premedicant and found it to be effective. Children readily accept both the placebo and fentanyl lollipops without any resistance. Our technique resulted in a significant increase in sedation and decrease in anxiety. The use of the fentanyl lollipop also resulted in children being more willing to separate from parents and in an improved quality of induction without prolonging the PACU stay. Although there was a significant change in respiratory rate, oxygen saturation remained well within the normal range during the entire preinduction and induction periods.

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Table 1: Separation and induction scores
(data reported as percent)

	Separation Scores			Induction Scores		
Group	1	2	3	1	2	3
Placebo	80	5	15	60	5	35
OTFC	75	25	0	75	20	5*

*Different from placebo by Chi Square analysis (p<0.05)

Title: COMPARATIVE HEMODYNAMIC EFFECTS OF EPIDURALLY ADMINISTERED SOLUTIONS OF ROPIVACAINE AND BUPIVACAINE PLAIN AND CONTAINING EPINEPHRINE IN THE DOG

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Ropivacaine is a new amide type local anesthetic whose anesthetic properties in animal experiments are similar to that of bupivacaine (1). This study examined the comparative hemodynamic effects of plain and epinephrine (EPI) containing solutions of ropivacaine (ROP) and bupivacaine (BUP) after epidural administration in the dog.

Methods. Approval by the Animal Research Committee was granted. Twelve adult male beagle dogs weighing 12.5 ± 0.4 kg ($\bar{x}$ ± SEM) were used. Under thiamylal anesthesia, catheters were implanted in the abdominal aorta, inferior vena cava and a jugular vein. An epidural catheter was implanted in the lumbar epidural space and attached to a Schraeder type valve which was sutured under the skin. Solutions of 1.0% ROP plain and containing 5.0 µg/ml EPI and 0.75% BUP plain and containing 5.0 µg/ml EPI were used. Three ml of test solution was injected, followed by a 0.5 ml flush of vehicle. Animals were randomly placed into two groups of six, one receiving BUP, the other ROP. All solutions were administered in a blind crossover fashion, such that each animal in a group received plain and EPI containing solution. Drug administrations were separated by 48 hours. Mean arterial blood pressure (MABP), heart rate (HR), cardiac output (CO), and other physiologic measurements were made at various time intervals during the experiment. Venous blood samples were analyzed for local anesthetic content by gas chromatography. Onset and duration of motor blockade was evaluated. Data compilation and analysis was done in a blinded fashion. Statistical analysis consisted of analysis of variance, Tukey's test and Student's 't' test for paired data where appropriate. Significance was attained at $p \leq 0.05$.

Results. (See Table)

1) All groups showed a decrease in HR. No difference existed between groups. However, only the plain solution of ROP significantly decreased HR. The QRS intervals were also significantly prolonged in this treatment group. This prolongation was significantly greater than that observed with the BUP plain solution. The PR interval was significantly prolonged in the ROP with EPI group. This prolongation was significantly different than the other groups.

2) All four groups demonstrated a similar but significant decrease in MABP. MABP spontaneously returned to pre-drug control values as the blockade wore off.

3) CO was significantly decreased to a similar extent in all treatment groups. The onset of significant depression in the EPI treatment groups occurred at a later time than in the plain solution treatment groups. In both ROP groups the duration of significant depression of cardiac output was longer than in the BUP groups.

4) Peak BUP concentrations occurred earlier than those of ROP. No differences in drug concentrations were observed between any of the treatment groups.

5) Onset and duration of motor blockade were not significantly different between drug treatment groups.

Discussion. The decreases in MABP and CO observed in the current study are probably related to the sympathetic blockade following epidural administration of ROP and BUP. The results suggest little difference in the degree or extent of sympathetic block between the two agents. Furthermore, EPI added to the local anesthetic solutions did not alter the degree of depression observed in MABP and CO but did postpone the onset of significant depression of CO. No animals required supportive treatment due to effects of test or control agent. There was no difference between 1.0% ROP and 0.75% BUP for either onset or duration of motor blockade.

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Average Maximum Percent Change From Control

	ROPIVACAINE		BUPIVACAINE	
	Plain	W/EPI	Plain	W/EPI
HR	-41	-35	-24	-33
MABP	-31	-27	-25	-29
CO	-49	-41	-37	-34
Cmax (µg/ml)	1.11	0.95	0.84	0.69
Tmax (min)	6.7	7.8	4.0	4.0
Motor block (min) onset	3.2	3.4	3.3	2.9
duration	234	251	190	255

Title: COMPARISON OF EPIDURAL AND GENERAL ANESTHESIA FOR LOWER EXTREMITY VASCULAR SURGERY: POSTOPERATIVE GRAFT FLOW RATES

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Introduction: Attention has recently been focused on epidural anesthesia for vascular surgery in reviews by Baron et al[1] and Raggi, et al[2] and a prospective study by Yeager et al[3]. These authors all commented on the safety and lack of postoperative complications associated with epidural anesthesia, but only Baron discussed the vasodilation during epidural anesthesia as contributing to improved operating conditions. Fuchs et al[4] reported vasodilation and increased collateral flow during arteriography under epidural anesthesia. The present study is designed to determine if the vasodilation and sympathetic blockade produced by epidural anesthesia would contribute to improved blood flow postoperatively.

Methods: Twenty-four adult patients (ASA Class 2-4) scheduled for procedures on the femoral-popliteal-tibial arterial system, who had no contraindication to the insertion of an epidural catheter (localized infection, septicemia, preoperative coagulopathy) and no major neurological deficit were studied. After appropriate institutional approval and informed, written consent patients were randomized to either receive general anesthesia (Group I, n=12) or epidural anesthesia (Group II, n=12). Preoperative laboratory data included CBC, serum electrolytes, creatinine and BUN, PT and PTT, ABG, EKG and chest x-ray. Preoperative medication was limited to diazepam (1mg/10Kg) or midazolam (0.2 to 0.3mg/10Kg). Two large-bore (14-16 ga.) intravenous catheters were placed. Five-lead EKG and non-invasive blood pressure monitoring were established. Invasive monitoring was utilized when clinically indicated. In Group I anesthesia was induced with thiamylal (3-5 mg/kg), tracheal intubation facilitated with succinylcholine (1 mg/kg) and maintained with N_2O/O_2 and enflurane. Muscle relaxation was obtained with vecuronium. In Group II an epidural catheter was placed in the mid to lower lumbar region (L_2-S_1) via an 18 ga. epidural needle and threaded 2-4cm cephalad. Following a test dose of 3cc of 1% lidocaine with epinephrine (1:200,000) 8 to 12cc of 0.5% bupivacaine was administered. Additional doses of 2-3cc 0.5% bupivacaine were administered to keep the analgesia level sufficient for the surgery. Fentanyl was administered for sedation. O_2 was administered at a rate of 2 LPM via nasal prongs. Heparin was administered upon the surgeon's request in a dose of 1 to 1.2mg/Kg. All aspects of postoperative care were under the direction of a staff surgeon. Mechanical ventilation was utilized postoperatively only when a need for respiratory support was noted. Blood flow in both lower extremities was measured by doppler and compared to ipsilateral brachial artery flow to obtain a flow index. This index was determined in each lower extremity preoperatively, immediately postoperatively, and on the first, fifth and tenth days postoperatively.

Results: There was no significant difference between the two groups for age, weight, height or pre-existing conditions. Average postoperative days in our hospital in Group I was 5.3 and in Group II, 5.9. No significant statistical difference existed between the two groups regarding postoperative complications. Both groups demonstrated a significant increase in blood flow in the operated extremity postoperatively. There was a quantitatively greater increase in flow in Group II but this did not achieve statistical significance. This quantitative difference persisted until the tenth postoperative day. Both groups also demonstrated an increased blood flow in the non-operated extremity, with Group II showing a much greater increase than Group I. Two of twelve patients in Group I required reoperation within 30 days for graft occlusion while no patients in Group II required reoperation.

Discussion: Improved surgical conditions for lower extremity vascular surgery under epidural anesthesia has been suggested recently.[1,4] Recent prospective data has suggested diminished postoperative morbidity and mortality with epidural anesthesia.[3] None of these studies focused on postoperative extremity blood flow. The present study suggests an advantage with the use of epidural anesthesia and indicates that further longer term study of the influence of anesthetic technique on the long term outcome of lower extremity vascular surgery is warranted.

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Title: A COMPARATIVE STUDY OF PROPOFOL AND THIOPENTAL AS INDUCTION AGENTS FOR CESAREAN DELIVERY

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Introduction In non-obstetric anesthesia propofol has been shown to offer advantages over the long-established induction agent thiopental sodium. However, the physiological and pharmacokinetic changes of pregnancy demand that detailed comparisons of the two induction agents be made in this situation before the routine use of propofol can be advocated for obstetric use.

Methods The protocol was approved by the University Medical Ethical Research Committee and verbal consent was obtained from all patients. Healthy women with an uncompromised, term pregnancy due to be delivered by elective Cesarean Section, were randomly allocated to receive either propofol or thiopental as an induction agent. Following preoxygenation and institution of left lateral tilt anesthesia was induced with either propofol or thiopental, the amount of drug given was determined by loss of eyelash reflex. Intubation was facilitated by succinylcholine 100 mg. Maintenance anesthesia was 50% oxygen in nitrous oxide reduced at delivery to 33%, supplemented throughout with halothane 0.5%. Muscle relaxation was provided by vecuronium 4 mg. Syntocinon 5 units and fentanyl 0.1 mg were given intravenously immediately after delivery.

EKG and arterial blood pressure were monitored automatically and recorded on paper at 1 min intervals until dilvery. End-tidal CO_2 and oxygen saturation were also continuously monitored. From a piece of double-clamped umbilical cord an arterial and venous sample were taken for pH and blood gas tensions, in addition an umbilical vein sample was collected for propofol/thiopental estimation. A maternal arterial sample was also taken at delivery for blood gas analysis and a venous sample taken at the same time for plasma propofol/thiopental levels. The Apgar scores of infants were recorded at 1 and 5 min from birth. Uterine tone was assessed by the surgeon on an unmarked 10 cm visual analogue scale (VAS). Recovery was timed from the end of anesthesia until response to commands. All patients were questioned 24 h later to ascertain any signs of awareness. Propofol and thiopental levels were measured by HPLC.

Values are expressed as mean ± SD. Significance values were calculated by unpaired 't' test, analysis of variance and linear regression as appropriate.

Results Ten patients received propofol and ten received thiopental. Both groups were comparable with regard to age, weight, period of gestation and preoperative hemoglobin and hematrocrit values. The mean induction dose of propofol was 2.1 ± 0.2 mg/kg and of thiopental 4.6 ± 0.9 mg/kg. The induction-delivery and uterine incision-delivery intervals were similar for both groups. Systolic blood pressure fell below 100 mmHg in four patients in the propofol group and 1 patient in the thiopental group. The changes in mean blood pressure during the induction-delivery period are shown in Figure 1. No patients in this study reported dreams or awareness during anesthesia.

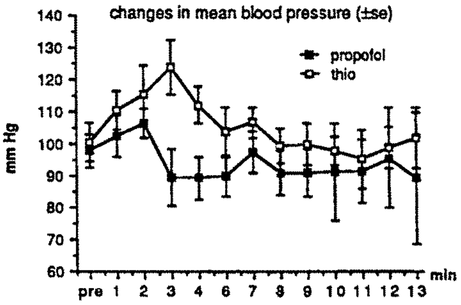
The Apgar Scores and blood gas analyses were similar for both groups. Recovery time was significantly shorter for the propofol series, 2.4 ± 1.2 min compared to 4.7 ± 1.6 min following thiopental ($p = 0.01$).

The mean propofol plasma level in the maternal vein was 1021 ± 552 ng/ml while in the umbilical vein it was 671 ± 370 ng/ml. The UV:MV ratio was 0.66 which is less than previously reported for thiopental (1) but similar to a previous study on propofol (2). There was a good correlation between induction-delivery interval and maternal propofol levels ($p < 0.05$) but not umbilical vein levels.

Table 1. Mean blood gas analysis (± SD) and Apgars

	Propofol (n=10)	Thiopental(n=10)
1 min Apgar(range)	7.0 (4-8)	6.9 (5-8)
5 min Apgar(range)	9.0 (8-10)	8.7 (8-9)
Mat pH	7.38 ± 0.4	7.39 ± 0.05
UV pH	7.26 ± 0.1	7.32 ± 0.03
UA pH	7.28 ± 0.1	7.26 ± 0.03
Mat pO_2	21.0 ± 3.6	25.5 ± 8.9
UV pO_2	5.5 ± 2.7	5.0 ± 1.8
UA pO_2	3.7 ± 1.4	2.9 ± 0.7
Mat pCO_2	4.6 ± 0.5	4.36 ± 0.83
UV pCO_2	6.6 ± 1.0	6.2 ± 1.1
UA pCO_2	7.1 ± 0.7	7.2 ± 1.3

Discussion Propofol appears to be a satisfactory agent for use in obstetric anesthesia. No difference in neonatal condition was observed between the two groups.



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Title: DOES CIMETIDINE EFFECT PLASMA LIDOCAINE LEVELS IN THE PARTURIENT?

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Introduction. Cimetidine is commonly used to reduce gastric acidity and has been recommended as prophylaxis against acid aspiration syndrome(1). Reports that it decreases the hepatic clearance of lidocaine(2) have favored the use of ranitidine. Lidocaine is often used in large volumes to provide satisfactory epidural analgesia for Cesarean section and therefore any interference in its elimination in the presence of cimetidine may increase the risk of toxicity. This study details the effect of cimetidine on plasma lidocaine levels during epidural anesthesia for Cesarean section.

Methods. Only healthy women at term who selected epidural analgesia for elective Cesarean section were included. They had no relevant past history and were not on any medication. Patient and Research Ethical Committee approval were obtained.

Patients were randomly allocated to receive either cimetidine 200 mg intravenously immediately before instituting the epidural block or no pretreatment. Lidocaine 2% with freshly added epinephrine 1:200,000 was the local anesthetic used. The dose was calculated as 6 mg/kg and was given over 5 min to provide satisfactory analgesia to the level of T6. Any patients requiring supplementary doses were eliminated from the study. Statistical analysis was by independent 't' test and analysis of variance (ANOVA). Venous blood was collected from an antecubital vein in the non-infused arm via a 16G cannula. Samples were obtained before any local anesthetic was given (control) and then at 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 120 min and at 3, 4, and 5 h after local anesthetic administration. A sample was taken from the umbilical vein at delivery. The samples were centrifuged and the supernatant plasma stored at -20°C until analysis. Lidocaine estimations were by HPLC with mepivacaine as the internal standard.

Results. Five patients were included in each group, and these were comparable in terms of age, weight and parity. Figure 1 shows that the administration of intravenous cimetidine prior to the administration of epidural blockade produces no effect on plasma lidocaine levels in the parturient. There was no significant difference between groups in the area under the plasma concentration time curve (AUC), umbilical vein levels, UV/MV ratios or Apgar score.

The 95% confidence intervals in this investigation are wide due to the large inter-subject variation in plasma concentrations and the small number of patients studied. If a difference in plasma concentrations of up to 35% were considered sufficient to show bio-equivalence then 5 patients in each group are enough to avoid a type II error.

Discussion. Treatment with cimetidine has been shown to affect the hepatic microsomal enzyme sytem P_{450} thereby decreasing the oxidative metabolism of drugs such as lidocaine. However, most reports have been demonstrated following repeat doses of cimetidine.

Hodgkinson stated that until further studies are available the administration of cimetidine prior to an epidural with amide local anesthetics is inadvisable as toxic levels may occur(3). Of particular concern are reports that cimetidine decreases liver blood flow and if so, the clearance of lidocaine could be reduced(2). In view of its high hepatic extraction ratio there is potential risk of local anesthetic toxicity.

This investigation has shown that a single dose of intravenous cimetidine does not affect lidocaine disposition. Moreover, the dosage of lidocaine used in this study did not produce any untoward side effects and plasma levels did not approach those levels associated wth toxicity.

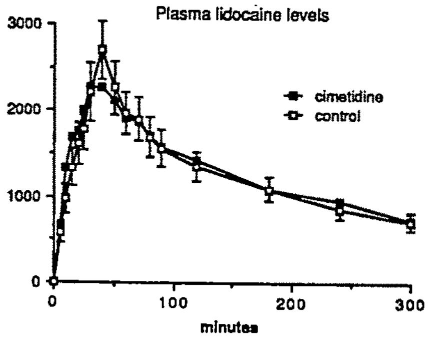

Figure 1. Mean plasma lidocaine levels (± SE).

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Title: ANALYSIS OF THE CLINICAL EXPERIENCE OF ANESTHESIA RESIDENTS

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Introduction. Evaluation of the clinical competence of anesthesia residents involves assessment of their knowledge and judgement, as well as their clinical and character skills. Development of these attributes requires that residents be exposed not only to an adequate number of patients during their training; but also that sufficient variety exists in their case loads to assure that each resident is experienced in the care of all types of patients. In an anesthesia program, where competition for certain types of cases may exist, available cases should be assigned in an equitable manner. Also, significant case variation among residents and areas of deficiency should be identified[1], so that adjustments in the clinical schedule can be made. Therefore, the purposes of this study was to determine the number of cases each resident was involved in during the second or third year of their residency; to determine the distribution of these cases according to the ASA physical class and surgical subspecialty; and to identify significant individual variation in caseload among the residents.

Methods. Data on each patient requiring anesthesia care in the main operating of a university hospital was extracted from individual computerized patient hospital files. This data included a demographic description of the patient, the primary diagnosis and procedure performed, the ASA physical class, and the anesthetic technique and personnel involved in the care of each patient.

Cumulative data was used to generate a monthly report on each resident throughout the second or third year of their anesthesia residency. This data was used to determine the clinical work load of individual second and third year anesthesia residents and to assess their exposure to different surgical subspecialties and different types of patients. Standardization of variables, principal components analysis and cluster analysis were used to identify outlying residents with caseloads that differed from other residents at the same level of training. Results are expressed as mean ± S.D.

Results. During the 12-month period under review, data was collected on fifteen second year and thirteen third year residents. Cases per resident was 428 ± 27 and 303 ± 23 for second and third year residents, respectively. The distribution of cases by ASA physical class and surgical subspecialty are shown in Figures 1 and 2. Standardization of variables, principal component analysis and cluster analysis identified both second and third year residents whose individual clinical experience varied in number or type of case when compared to the group as a whole.

Figure 1
Distribution of Cases by ASA Physical Class

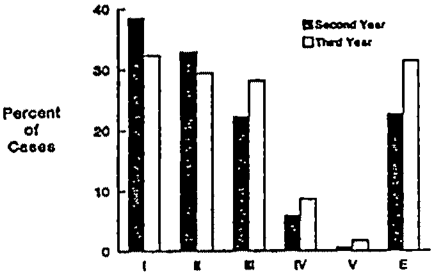
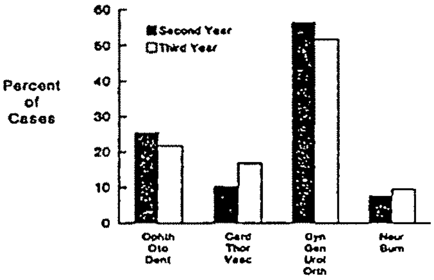


Figure 2
Distribution of Cases By Surgical Procedure



Discussion. Competence in anesthesiology can be measured, in part, by written or oral examinations and by resident evaluations completed by clinical competence committees. However, these methods of evaluation may not adequately evaluate a resident's clinical experience.

Competence generally develops as experience is accumulated, therefore the number and types of cases residents complete during their program may also provide a measure of competence, although minimum standards have not been defined. This study describes the number and types of patients cared for in one anesthesia program and identifies individual outliers. From this study we conclude that:

1. the numbers and types of cases done by residents during the course of their training may vary and individual outliers can be identified;
2. senior residents care for patients with more complex medical problems.

Monitoring of resident caseloads may ensure that each resident has an opportunity to participate in the care of all types of patients.

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Title: DAILY EVALUATION OF ANESTHESIA RESIDENT'S CLINICAL PERFORMANCE

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Introduction. Traditionally, ABA in-training and oral exams are used to assess the fund of knowledge of anesthesia residents. However, these techniques fail to evaluate characteristics considered important to the practice of Anesthesia. Performance rating evaluations have been found to be useful in several areas of medical education; but their application to education in anesthesia has been limited.$^{2-5}$ We have recently developed and implemented a daily evaluation system for anesthesia residents. The initial results were used to determine whether this evaluation system could reliably distinguish between second year and third year residents.

Methods. From an initial list of 72 characteristics of a physician, the faculty selected those attributes considered to be most important in an anesthesiologist. Three major categories were identified Knowledge and Judgement, Technical Skills, and Personal Characteristics. Each of these categories were subdivided into a number of specific characteristics. Residents were evaluated on a daily basis by the faculty member working with them. In each of the three major categories, the faculty observed and reported the residents performance. Subscores in seven knowledge and judgement areas and nine technical skills were rated as 1 = "outstanding"; 2 = "above average"; 3 = "average"; 4 = "marginal" or 5 = "unsatisfactory". The faculty also rated personal characteristics "satisfactory or unsatisfactory". In addition, an overall performance score was assigned for each major category. The evaluation forms were scanned optically, and the stored information in a computer database. Residents received a monthly summary of their performance.

Results. 14 second year and 16 third year anesthesia residents were evaluated by 34 faculty members over a nine month period.

During the initial seven month period, 1519 forms were returned. The mean of the knowledge and judgement subscores for the second and third year residents were 2.67 ± .18 and 2.06 ± .29, respectively. The means for technical skill was 2.64 ± .16 and 2.03 ± .23, respectively. There was a significant difference in mean scores for knowledge and judgement and technical skills between second and third year residents ($p < 0.01$) (Figs I and II).

Figure I: Mean score on knowledge and judgement category of individual residents

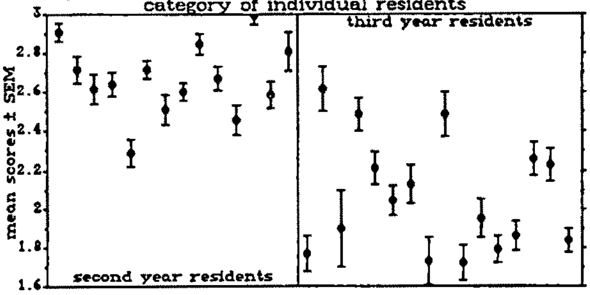
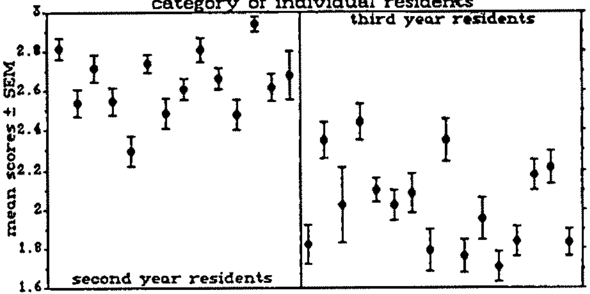


Figure II: Mean scores on technical skill category of individual residents



The Overall Performance score improved among the third year residents from an average of 1.98 during the first two months to 1.80 during the last two months ($p < .02$). The Overall Performance score was not significantly different for second year residents during the same interval.

The average number of evaluations of each resident was 61.6 ± 7. 16.6% of the evaluations were discussed by the evaluator with the individual resident at the time the evaluation was completed. The number of evaluations received did not differ significantly between better and poorer performing residents.

Discussion. In an effort to assess clinical performance of our anesthesia residents, we have designed an evaluation system which is used to monitor resident's progress on a daily basis in knowldge and judgement, technical skills and personal characteristics. The knowledge and judgement characteristics were significantly different between residents in the second and third year groups. Significant improvement in scores occurred over the seven month period among the third year residents. In our initial analysis, we found no significant difference in the number of evaluations submitted or in the discussion frequency between residents who achieved higher or lower ratings on daily evaluations. This initial report indicates a daily evaluation system of anesthesia residents may be useful to assess noncognitive clinical performance important to the practice of anesthesia.

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Title: PHARMACOKINETICS OF DOXACURIUM CHLORIDE (BW A938U) IN PATIENTS WITH ORGAN FAILURE

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Introduction. Doxacurium chloride (BW A938U), a new nondepolarizing neuromuscular blocking agent, has a long duration of action and minimal cardiovascular side effects (1). The relative role of the liver, the kidney, and plasma cholinesterase in the elimination of doxacurium has not yet been determined. The purpose of this study was to determine the effects of hepatic failure and renal failure on the pharmacokinetic profiles of a single intravenous injection of doxacurium.

Methods. Twenty-seven surgical patients, 18 - 55 years old, requiring invasive monitoring as appropriate anesthetic care were entered into this study. This study was approved by the Institutional Review Board; informed, written consent was obtained from each patient. Nine patients (ASA Class III & IV) had end-stage liver disease and were to undergo hepatic transplantation; 9 patients with end-stage renal disease (ASA Class III) were to undergo renal transplantation; 9 other patients (ASA Class I & II) without known liver or renal disease served as controls. No patient in the liver transplantation group had overt preoperative renal failure; the highest serum creatinine level obtained was 1.5 mg/dl in one patient. All patients with renal failure underwent dialysis within 48 hours of transplantation. The mean weights for the control patients were 81.7 ± 10.8 kg, (mean ± SD) the patients with renal failure 72.9 ± 11.1 kg, and the patients with hepatic failure 64.3 ± 9.4 kg.

Anesthesia was induced with fentanyl (1-4 µg/kg) and thiopental (2-4 mg/kg). Incremental doses of fentanyl were used to maintain anesthesia together with isoflurane in either N2O:O2 or air:O2. Endotracheal intubation was facilitated by the administration of 1-2 mg/kg succinylcholine. End-tidal isoflurane concentrations were maintained at or below 0.8% using a mass spectrometer. Ventilation was controlled to maintain end-tidal CO2 at 35-40 mm/Hg. Blood pressure was monitored directly with the use of an indwelling radial arterial catheter. ECG, O2 saturation, and temperature were monitored and recorded on all patients.

Following induction of anesthesia, neuromuscular function was monitored by supramaximal stimulation of the ulnar nerve at the wrist with repetitive trains-of-four stimuli (2 Hz for 2 sec at 20 sec intervals) using surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan Bennett/Datex monitor.

Thirty-45 minutes after the administration of succinylcholine and after recovery of neuromuscular transmission, a single bolus injection of doxacurium (0.015 mg/kg) was made through a peripheral intravenous catheter over a 5-10 second period. Blood pressure and heart rate were recorded at 1, 3, 5 and 9 minutes following administration of the drug. Blood samples were drawn from the arterial catheter at 0, 2, 4, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240 and 360 minutes. The blood samples were mixed with EDTA and phenylmethyl sulfonyl fluoride (a pseudocholinesterase inhibitor), centrifuged, and the plasma decanted and frozen to -60° C. Urine was collected for 6-12 hours to estimate renal excretion and clearance of doxacurium in those patients undergoing hepatic transplantation and those patients acting as controls.

Doxacurium concentrations in plasma and aliquots of urine were quantified by high pressure liquid chromatography with appropriate internal standards. Mean residence time (MRT), clearance (CL), and volume of distribution at steady state (Vdss) were calculated by noncompartmental data analysis using standard formulae. The area under the curve (AUC) at infinity was estimated by the trapezoid rule; the AUC at the last data point averaged 81% of the area at infinity.

Results. The pharmacokinetic parameters of doxacurium in patients with hepatic failure, renal failure and those acting as controls are listed in Table 1. One patient was eliminated from the hepatic failure group due to a probable inadvertent error in dosage. None of the pharmacokinetic parameters of doxacurium differed significantly from each other, although there was a large amount of variability within groups. About 25-30% of the administered dose of doxacurium was recovered in the urine in those patients with hepatic failure and those serving as controls. There was no correlation between the pharmacokinetic parameters and serum albumin, GGTP or creatinine levels.

There was no significant difference between groups in the following parameters of neuromuscular function: maximum block obtained (MxBk%); time till 25% recovery of neuromuscular transmission (T25 mins) time till 75% recovery (T75 mins) and recovery index 25-75% (RI mins) (Table 2). The duration of doxacurium action was more variable in the renal failure group.

Discussion. Neither hepatic failure nor renal failure were associated with any significant differences in the kinetic parameters of doxacurium. There was, however, a trend towards decreased CL in renal failure patients relative to control. Decreased CL may prolong the neuromuscular effect of doxacurium in individual patients. Renal clearance of doxacurium was similar in patients with hepatic failure and those serving as controls.

Thus doxacurium, a highly potent long acting neuromuscular blocking agent with minimal cardiovascular side effects would seem to have a useful role in anesthesia for long procedures in patients with hepatic and renal failure.

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Table 1. Doxacurium Pharmacokinetic Parameters

PHARMACOKINETIC PARAMETERS	CONTROL PATIENTS	HEPATIC FAILURE PATIENTS	RENAL FAILURE PATIENTS
MRT (min)	37.2 ± 25.1	73.8 ± 28.1	222.0 ± 28.1
CL (ml/kg/min)	2.7 ± 1.1	2.5 ± 0.7	1.8 ± 0.7
Vdss (ml/kg)	83.0 ± 35.5	168.6 ± 44.5	214.0 ± 125.0
Renal clearance	0.6 ± 0.6	0.8 ± 0.7	----------

All values are mean ± SD

Table 2. Neuromuscular Function Parameters

	CONTROL PATIENTS	HEPATIC FAILURE PATIENTS	RENAL FAILURE PATIENTS
Max Block (%)	86.1 ± 16.7 (9)	67.8 ± 35.0 (8)	85.9 ± 7.1 (8)
T_{25} (mins)	36.1 ± 20.6 (7)	51.6 ± 29.5 (4)	63.2 ± 55.6 (5)
T_{75} (mins)	54.9 ± 30.2 (8)	75.1 ± 47.9 (6)	53.2 ± 37.0 (2)
RI (T_{25-75} mins)	31.2 ± 29.3 (6)	56.2 ± 11.6 (3)	34.1 ± 23.2 (2)

( ) = number of patients providing data

TITLE : MOLECULAR ACTIONS OF RACEMIC KETAMINE ON SINGLE SODIUM CHANNELS FROM HUMAN BRAIN CORTEX.

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Introduction: Sodium channels are membrane proteins responsible for the generation of fast propagated action potentials. These proteins play a vital role in neuronal signal integration and cell communication. Recently, it has been shown that at least two of the functions of human brain sodium channels are affected by clinically relevant doses of pentobarbital (1). Ketamine is structurally unrelated to pentobarbital and produces anesthesia with very different clinical qualities. It is of interest, therefore, whether pentobarbital and ketamine also differ in their molecular actions on sodium channels.

Methods: Approved by the institutional Committee on Human Rights in Research, human cortical tissue samples were obtained from patients undergoing craniotomies for removal of diseased (tumorous) and non-diseased (aneurysm and hydrocephalus) tissue and immediately frozen; membrane vesicles in the form of synaptosomes were prepared and incorporated into planar lipid bilayers in the presence of 0.25 uM or 1.0 uM batrachotoxin (2). Single sodium channel currents were recorded under steady-state voltage-clamp conditions. The control behavior of single sodium channels (current-voltage curves, fractional open time, total closed time, steady-state voltage activation) was established for 30 - 40 minutes. Between 0.05 mM and 9.1 mM of racemic ketamine was subsequently added to either the extracellular or intracellular electrolyte in the presence of the same channel. The electrophysiological measurements were repeated and continued until the membrane broke spontaneously, typically after several hours.

Results: Sodium channels from diseased and non-diseased brain tissue showed no statistically significant difference in their properties (2).

1. Immediately after ketamine addition to the aqueous phase, the channels began to open and close very rapidly (at a rate greater than 50 Hz) at all administered doses. This led to a membrane potential independent decrease in the fractional open time. The dose-response curve followed a rectangular hyperbola. A weighted computer fit yielded a maximal average conductance suppression of 71.1% and a K_{50} of 1.1 mM (Fig. 1).
2. Maximal single channel current amplitudes appeared not to be affected by ketamine.
3. Long complete closures (> 0.4 s) were observed more often and yielded an average total closed time of 5.7% (± 1.6%; S.D.) at all administered doses.
4. Ketamine introduced at either side of the channel gave similar results.
5. Ketamine destabilized normal steady-state activation behavior, producing a shallower slope of the activation curve. The midpoint potentials ranged much more widely in the presence of ketamine and were shifted to more negative potentials.
6. Different batrachotoxin concentrations (0.25 uM and 1.0 uM) revealed no statistically significant differences in any of the measured single channel characteristics, both in the presence and absence of ketamine.

Conclusion: Like pentobarbital, ketamine affects at least two primary functions of sodium channels: a voltage-independent reduction of the fractional channel open-time by induction of fast flickering as well as long complete closures, and an interaction with the voltage-dependent steady-state activation behavior of the sodium channel (1). Similar results with different batrachotoxin concentrations suggests no major role for this channel activator in the observed drug effects. In contrast to pentobarbital, the concentrations used were considerably higher than those encountered during clinical anesthesia (0.01 - 0.02 mM) (3). However, other ion channels are affected by clinical doses of ketamine, as has been demonstrated for the acetylcholine receptor (4). These present studies contribute a first step in an attempt to correlate different types of anesthesia observed clinically with differential actions of anesthetics on human ion channels.

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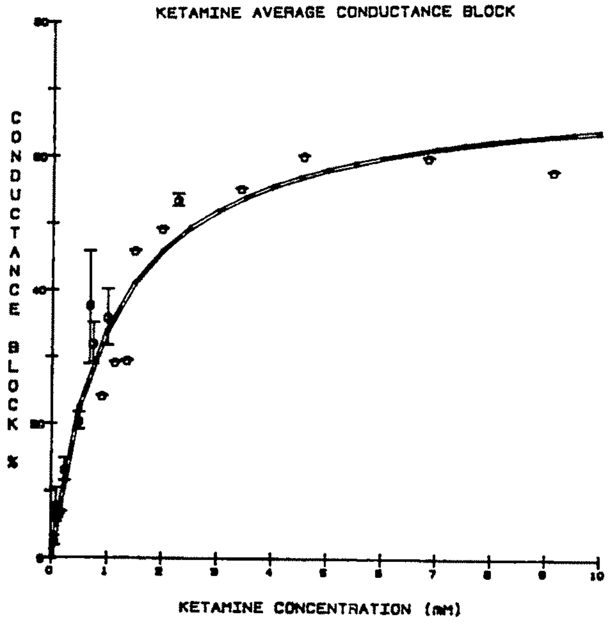
FIGURE 1



Title: GLUCOSE CHANGES DURING PANCREAS TRANSPLANATION

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Introduction: Pancreas transplantation has become a popular technique in the management of Type I diabetes mellitus. Although more than 1,000 human pancreas transplantations have been performed at more than 80 institutions, little has been written about intraoperative management. Although anesthetic management is quite similar to renal transplant recipients,[1] there are some expected fundamental differences. One of the major concerns during pancreas transplantation is abrupt changes in the serum glucose. The normal pancreas contains β cells which secrete insulin in response to hyperglycemia and α cells which secrete glucagon in response to hypoglycemia. Just how rapidly this feedback loop becomes operational after recirculation following up to 18 hours of hypothermic, ischemic storage is unknown. In addition, the exact constitution of the intitial venous effluent from the donor pancreas has not been reported.

It is known that hyperglycemia can cause irreversible damage to the β cells.[2] Therefore, tight control of serum glucose during transplantation may well affect the future function of that organ.

Methods: We retrospecitvely reviewed the records of nine patients with Type I diabetes mellitus who presented for pancreas transplantation. The study met the requirements of the Institutional Review Board. Seven patients received combined pancreas and renal transplants and two had previous renal allografts functioning well and received pancreas transplantations only. All received immunosuppressive medications preoperatively including 3 mg/kg methylprednisolone. All received a whole organ transplant with a cuff of duodenum implanted into the bladder with vascular anatomoses to the iliac vessels. All patients were anesthetized with isoflurane and fentanyl and were monitored with arterial and central venous pressure lines. Patients were placed on a continuous insulin infusion shortly after admission to the hospital and the infusion was maintained perioperatively based on serum glucose according to a protocol (see table). All glucose containing solutions were avoided unless serum glucose decreasead below 60 mg/dl. Blood samples for serum glucose were drawn at 30-minute intervals throughout the case, except for the first hour after recirculation, during which time samples were drawn every 10 minutes. The insulin infusion was adjusted after each serum glucose determination. Data were analyzed using the paired t-test. $P < 0.05$ was considered significant.

Results: Serum glucose data is shown in the figure.

Discussion: Glucose dynamics in pancreas transplant recipients is a complex interaction of exogenous steroid administration, stress response to anesthesia and surgery, exogenous insulin infusion, administration of dextrose containing solutions, and the unpredictable level of function of the transplanted organ superimposed on a patient with abnormal glucose metabolism.

Our data show a stable intraoperative course utilizing a regimen of continuous insulin infusion strictly adhering to a protocol based on the serum glucose and intravenous solutions without dextrose. A statistically significant rise in serum glucose after recirculation was rapidly controlled by adhering to the insulin infusion protocol.

There are several factors which could account for the observed rise in glucose. This could represent glucose contained in the preservative (300–400 mg/dl) and released into the recipient with recirculation. It could also be due to an inappropriate release of glucagon by the donor organ or the effects of the steroids contained in the preservative.

Although our observed rise in glucose after recirculation was statistically significant, it was a fairly modest rise in three of the nine patients. Thus, whatever mechanisms account for the change are inconsistent and the importance of intraoperative glucose monitoring is clear.

We conclude that an intraoperative glucose management consisting of nonglucose containing solutions, a continuous insulin infusion based on an algorithm and frequent sampling of serum glucose results in stable glucose dynamics in pancreatic transplant recipients.

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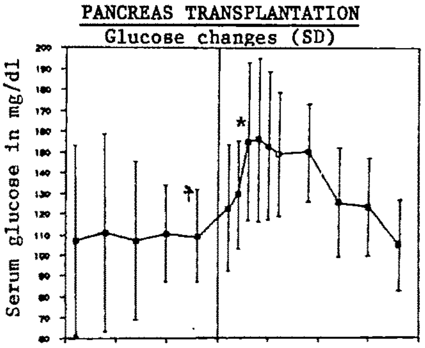
Table

INSULIN INFUSION PROTOCOL

Blood Glucose (mg/dl)	Insulin Infusion Rate (U/hr)
Greater than 250	3.0
200-249	2.5
150-199	2.0
120-149	1.5
100-119	1.0
70-99	0.5
Less than 70	0.2

Figure


PANCREAS TRANSPLANTATION

Glucose changes (SD)

Time (min) 0=recirculation of graft

*Significantly different from † (paired t-test)

Title: ESMOLOL INFUSION DEPRESSES LEFT VENTRICULAR FUNCTION IN DOGS ANESTHETIZED WITH ISOFLURANE

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Introduction: Esmolol is a beta-1 antagonist which has recently been introduced to treat supraventricular tachycardia and hypertension. It has been shown to depress left ventricular contractility in the awake dog in a dose related manner.(1) However, there are no data on the hemodynamic effects that result from the interaction between esmolol and isoflurane, an anesthetic also capable of causing myocardial depression. This study was designed to determine if an extreme degree of myocardial depression occurred when esmolol is administered during isoflurane anesthesia.

Methods: This protocol was approved by the Animal Research Committee. Twelve mongrel dogs weighing 20± 1 kg were anesthetized with thiamylal 3 mgs/kg and the trachea was intubated. Anesthesia was maintained with isoflurane 1.4% end tidal in 100% oxygen and the dogs were mechanically ventilated to an end tidal CO_2 of 30-34 mm hg; both gases were measured by an infrared airway gas monitor. A catheter was inserted into the femoral artery to measure systemic pressure and into the pulmonary artery to measure pulmonary artery (PA); pulmonary capillary wedge (PCWP), central venous (CVP) pressures and cardiac output (CO). A micromanometer tipped catheter (Millar-350), was inserted retrograde into the left ventricle (LV) via the right carotid artery for direct LV pressure measurements and electronic derivation of LV dP/dt. The maximum LV dP/dt was taken as the peak positive deflection on the LV trace. Heart rate (HR), systemic, PA and LV pressures, and LV dP/dt tracings were continuously recorded. SVR was calculated by standard formula. When blood pressure, PA pressure, end tidal CO_2 and isoflurane concentration had stabilized for at least twenty minutes, control measurements (baseline-1) were taken.

A 500 mcg/kg bolus of esmolol was then administered over one minute and an infusion was continued at 100 mcg/kg/min for twenty minutes. Measurements of the above hemodynamic parameters were repeated at 1,5,10,15 and 20 minutes. The 20 minute measurement was also used as baseline-2 for statistical comparison. Another bolus of esmolol, 500 mcg/kg was given over one minute and the infusion rate was increased to 300 mcg/kg/min. Repeat measurements were obtained at the same time intervals as noted above. This 20 minute value was used for baseline-3. The infusion rate was increased to 500 mcg/kg/min for 20 minutes. Hemodynamic measurements were obtained at the same time periods as noted for the lower infusion rates. Statistical significance of change from baseline was assessed by repeated measured ANOVA and paired t- tests with alpha (2-tailed) set at p 0.05.

Results: (see Table) During esmolol infusion, the decrease in mean BP, 27%, achieved statistical significance from baseline only at the highest dose, 500 mcg/kg. There were no significant changes from baseline at the lower doses. LV dP/dt max. depression from baseline was statistically significant, 19%, at the lower dose and 38% at the highest dose. C.O. was also significantly reduced from 20% to 42% compared to baseline as the infusion dose increased. HR progressively decreased throughout the study to 17% lower than baseline at the termination of the observation period. There were essentially no statistically significant changes in PCWP, CVP or SVR.

Discussion: Previous investigators have demonstrated that esmolol can cause moderate ventricular depression in the unanesthetized dog,(1) as well as dogs anesthetized with enflurane (2). In contrast, humans anesthetized with fentanyl (3) did not experience any significant myocardial depression. The effects of esmolol administration during isoflurane anesthesia, have not yet been evaluated. This interaction is of considerable clinical interest since isoflurane is a commonly used anesthetic and the frequency of esmolol administration is increasing. Since the hemodynamic effects of isoflurane can differ considerably from fentanyl and enflurane, one cannot extrapolate from those previous studies to predict what will happen with the esmolol-isoflurane interaction. These data indicate that this combination does produce a statistically significant decrease in myocardial contractility which is dose related. It is interesting to note that while left ventricular function decreased at all doses of esmolol, as evidenced by decreases in LV dP/dt and C.O., BP did not decrease until the highest dose level was reached. This suggests that BP was maintained in the face of reduced contractility by compensatory vasoconstriction.

In conclusion, esmolol infusion during isoflurane anesthesia does depress LV contractility. Therefore, this drug combination should be used with caution in clinical situations where myocardial dysfunction exists or can easily develop, or when the drug is administered at the higher dosage used in this study.

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Table	Maximum Change from Baseline		
	Dose=100	Dose=300	Dose=500
Mean BP	- 4%	-14%	-24%**
LV dP/dt	-19%*	-35%*	-38%*
C.O.	-20%*	-34%**	-42%**
H.R.	-10%**	-14%***	-17%**

Dose=mcg/kg/min *p .05 **p .01 ***p .001

Title: USE OF DILEVALOL IN THE TREATMENT OF POSTOPERATIVE HYPERTENSION

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Introduction. Hypertension is a significant complication seen in the post-anesthesia recovery room. Postoperative hypertension may precipitate left ventricular failure, pulmonary edema, myocardial ischemia, or hemorrhagic complications. Hypertension in this setting is usually treated with vasodilators, such as hydralazine, or beta blockers, such as labetalol.[1] Dilevalol, an optical isomer of labetalol, is a new drug currently being investigated for the treatment of chronic hypertension. The intravenous form of dilevalol may be useful in the management of acute hypertension. Dilevalol's antihypertensive action is mediated by two separate effects: (1) non-selective blockade at the beta$_1$ receptor, and (2) an agonistic effect at the beta$_2$ receptor.[2] The former decreases myocardial inotropy and the latter results in vasodilation. This study was undertaken to determine the safety and efficacy of intravenous dilevalol in the treatment of acute postoperative hypertension.

Methods. Eighteen patients with a history of hypertension were studied in the immediate postoperative period. Institutionally approved informed written consent was obtained during the preoperative visit. Exclusion criteria were: contraindications to beta blockers, CVA within 6 months, MI within 3 months, and childbearing potential. Common causes of postoperative hypertension such as pain, hypoxia, hypercarbia, or a full bladder were treated or excluded. Treatment was initiated when systemic blood pressure was ≥ 180/105 mm Hg on three consecutive readings at five minute intervals in the post-anesthesia recovery room. The goal of treatment was to achieve a systolic blood pressure < 160/90 mm Hg at two consecutive 5 minute intervals. Blood pressures were recorded by an automated oscillometric blood pressure device at five minute intervals following intravenous administration of dilevalol. The ECG was continuously monitored. The initial dose of dilevalol was 10 mg, followed by 20 mg, 50 mg, 100 mg, and 200 mg (x2) as needed to control blood pressure to a maximum dose of 580 mg. If a given dose of dilevalol did not produce the desired effect within 10 minutes, then the next incremental dose was administered. When a systolic blood pressure < 160 mmHg was recorded for two consecutive readings, administration of dilevalol was terminated. Statistical analysis was performed using repeated-measures analysis of variance and significance was defined as $P < 0.05$.

Results. In the series of 18 patients, 11 patients completed the protocol as described. No patient required the 200 mg dose of dilevalol. Results for these patients are shown in the Table. In the remaining 7 patients, the incremental dosage was reduced at the discretion of the investigator to avoid hypotension. These patients are not included in the data analysis. Six of these 7 patients responded with a satisfactory reduction in blood pressure. One hour following the last dose of dilevalol, 5 out of 11 responders analyzed, and none of the remaining 6 responders, had a systolic blood pressure < 160 mm Hg. No major side effects were observed. Minor side effects seen were nausea (2 patients) and a burning sensation at the IV site (1 patient).

Discussion. Dilevalol is a new antihypertensive agent that is effective with chronic oral administration. While closely related to labetalol in its chemical structure, it has negligible alpha-blocking properties. It is unique among beta-blockers in that it results in beta$_2$-mediated vasodilation. Oral administration has been studied, but the safety and efficacy of intravenous dilevalol has not previously been described. While the results of this study are preliminary, the data indicate that dilevalol merits further investigation as an intravenous antihypertensive agent in the perioperative period.

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Table

HEMODYNAMIC EFFECTS OF IV DILEVALOL

Dose		Time post-dose	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)
	N=11	Baseline	187±13	107±14	78±11
10 mg	N=11	5 min	176±27	104±15	68±9*
	N=11	10 min	177±17	100±15	68±10*
20 mg	N=10	5 min	167±11*	92±13*	71±8*
	N=10	10 min	166±18*	92±14*	70±9*
50 mg	N=8	5 min	156±14*	91±12*	69±4*
	N=8	10 min	164±13*	89±12*	68±5*
100 mg	N=3	5 min	154±5 *	82±11	69±5
	N=3	10 min	158±5 *	84±14*	70±4

Means ± S.D. * $P < 0.05$ compared to baseline

Title: EFFECTS OF HALOTHANE ON VENTRICULAR TACHYCARDIA IN INTACT DOGS

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Introduction. Halothane is usually considered a proarrhythmic agent because it sensitizes the heart to the arrhythmic effects of catecholamines[1]. However, in-vitro, halothane decreases spontaneous activity in infarcted canine cardiac tissue[2]. Ventricular tachycardia (VT) may be produced by several electrophysiologic mechanisms. We determined the effects of halothane on 4 different types of VT in an in-vivo canine model[3].

Methods. This study was approved by the Institutional Animal Care Committee.
Model 1: Abnormal automaticity. VT due to abnormal automaticity arising from partially depolarized ischemic cells was observed 24 hours after dogs anesthetized with pentobarbital, 30 mg·kg^{-1} underwent ligation of the left anterior descending coronary artery (LAD) with placement of interscapularly exteriorized atrial and ventricular epicardial pacing wires and a left atrial catheter.
Model 2: Reentrant VT. Survivors from Model 1 recovered for one week. ECGs were recorded daily to condition the dog. On the day of the experiment programmed electrical stimulation (PES) was performed to induce reentrant VT. PES consisted of double or triple premature extrasystoles during ventricular pacing at 300 or 400 msec cycle lengths (CL).
Model 3: Triggered automaticity induced by Delayed After Depolarizations (DAD). Dogs were instrumented as in Model 1 but the LAD was not ligated. After one week, triggered automaticity was induced using ouabain 40 ug·kg^{-1} IV (intravascularly via left atrial catheter) followed by 10 ug·kg^{-1} IV q 10 min until VT occurred. Ouabain was then given 10 ug·kg^{-1} q 30 min to maintain toxic ouabain levels.
Model 4: Triggered automaticity induced by Early After Depolarizations (EAD). Dogs were instrumented as in Model 3. One week later, dogs were given CsCl$_2$, 1mM·kg^{-1} IV. CsCl$_2$ was then continued by infusion at a variable rate to maintain toxicity.

In each model, after a stable dysrhythmia was induced, halothane was administered by mask from a calibrated vaporizer at 0.5, 1, 2, and 4% in 100% O$_2$. The animal was intubated if left atrial blood gases showed respiratory acidosis.

Results. Model 1: Seven dogs underwent LAD ligation. Each of five surviving dogs demonstrated incessant VT (94.7±2.3% of beats of ventricular origin). Halothane 0.5%, 1% and 2% reduced ventricular beats to 91.9±3.3%, 75.5±18.9% and 34.8±15%, respectively ($P<0.05$). Heart rate did not change. 1% halothane restored sinus rhythm in one dog, 2% in one and 4% in one. In one of the remaining two, 2% halothane reduced ventricular beats from 100% to 35.9%. In the other, 4% halothane increased sinus beats from 7% to 20%.
Model 2: Six dogs recovered for one week following LAD occlusion. In each animal, repetitive extrasystoles of presumed reentrant origin could be induced by PES. In 3 dogs, halothane 1% eliminated the inducible extrasystoles. In these dogs ERP increased by 23% during halothane. In one dog, more severe VT occurred after halothane (Fig 1). ERP was only prolonged by 8% in this dog. In another dog, ERP increased by 8% and no change in VT severity occurred. Sustained monoform VT was induced in one dog. Halothane 1,2 and 4%, had no effect on this VT which degenerated to VF following attempted cardioversion.
Model 3: Halothane was uniformly beneficial in reducing the severity of triggered VT in five dogs made ouabain toxic. Sinus rhythm was restored during 1% halothane in two dogs, 2% in two and 4% in one dog. These changes were reversible.
Model 4: CsCl$_2$ produced multiform VT which often degenerated to Torsades des Pointes and VF. Halothane 1, 2 and 4% had no effect on these EAD triggered arrhythmias.

Discussion: This study demonstrates that halothane has diverse effects upon different VT mechanisms. Halothane decreases the severity of VT due to abnormal automaticity and DAD triggered automaticity. Both these mechanisms depend upon calcium influx which is blocked by halothane[4]. Halothane had no effect on CsCl$_2$ EAD triggered VT which depends upon a Na$^+$ current. Halothane, which slows conduction and increases ventricular ERP, produced both pro- and antiarrhythmic effects on reentrant VT which correlated with changes in ERP.

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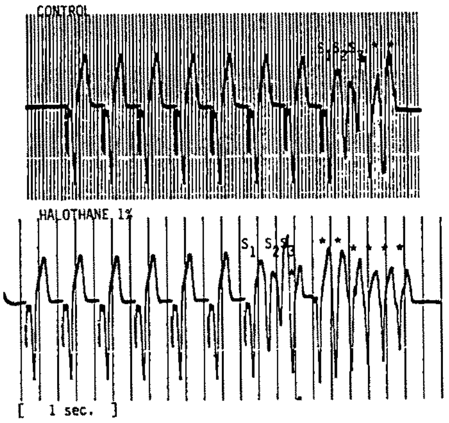

Figure 1: Proarrhythmic Effects of Halothane. One week after LAD ligation, PES induced 2 extrasystoles (*). Halothane 1% increased ERP from 130 to 140 msec and 7 beat runs of VT resulted. S1=basic drive (400 msec); S2, S3=premature extrastimuli.

Title: A COMPARISON OF PATIENT-CONTROLLED EPIDURAL ANALGESIA AND INTERMITTENT "TOP-UPS" DURING LABOUR

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Introduction. In recent years patient-controlled administration of analgesics has gained in popularity with the advent of safer and more sophisticated delivery systems, as well as an increase in patient awareness of the technique. Different routes of administration, including intravenous, intramuscular and epidural, have been used.[1,2,3] Epidural local anaesthetics administered by the parturient using a PCA device during labour has been described[4]. The purpose of this study is to compare PCEA with the more conventional technique of intermittent local anaesthetic "top-ups" during the first stage of labour.

Methods. Approval was obtained from our University and hospital ethics and research committees and each patient signed an informed consent. ASA physical status I or II nulliparous parturients, requesting epidural analgesia in early labour, were selected. Each patient was randomly assigned to one of two groups. Each patient in both groups received an initial dose of 8 mls 0.25% bupivacaine (in divided doses) through their epidural catheter.

Group A patients self-administered epidural increments of 4 ml 0.125% bupivacaine with 1:400,000 epinephrine using an Abbott Life Care® PCA Infuser. A lock-out time of 20 minutes was pre-set thus limiting the hourly maximum dose to 12 mls.

Group B patients received intermittent doses of 12 mls 0.125% bupivacaine with 1:400,000 epinephrine, when requested, and given by the anesthesiologist.

Patients were assessed hourly and the following information recorded; visual linear analogue pain and satisfaction scores using a 10 cm scale, segmental sensory level, degree of motor block, maternal blood pressure, frequency of contractions, cervical dilatation and fetal heart rate.

Patients in group B were also assessed prior to each "top-up" in terms of pain and satisfaction scores at that time.

Group A patients were asked to retrospectively record their maximum pain and satisfaction scores between hourly assessments.

Other collected data included the duration and outcome of labour, neonatal Apgar scores and the dose of bupivacaine used. Supplementary analgesia for persistent back pain or unilateral block consisted of 0.25% or 0.5% bupivacaine.

Results. Thirty-three patients have been studied so far, 17 in group A and 16 in group B. Patients were similar with respect to age, weight, height, parity, cervical dilatation at epidural insertion and gestational age. The mean length of duration of the first and second stages of labour were similar in both groups. The forceps and Caesarean section rates were the same in both groups. The mean hourly dose of bupivacaine required in group A was 5.3(SD ± 1.3) mg and in group B 5.6(SD ± 1.8) mg. This difference is not statistically significant.

Figure 1 shows that the two groups achieved similar degrees of pain relief and satisfaction during the study at fixed hourly intervals, but an increase in the variation of pain relief is more marked when pain scores prior to "top-ups" are included. Patients in group B had a less consistent pattern of pain relief when compared with group A patients, (see table)

Pain Score	Group A (PCEA	Group B (CIT)
< 3	32	11
> 3 < 5	2	6
> 5	2	11
	36 = no. of observations made between fixed hourly assessments	28 = no. of observations made before "top-ups"

No complications arose as a result of using the PCA device.

Conclusions. Pain relief during labour can be adequately achieved with a PCEA technique. Very low hourly local anaesthetic requirements were seen in both groups. Group A patients were able to titrate a more consistent level of analgesia during labour. Conventional intermittent "top-ups" of local anaesthetics during labour may be associated with delays that can cause a return of labour pain to significant levels.

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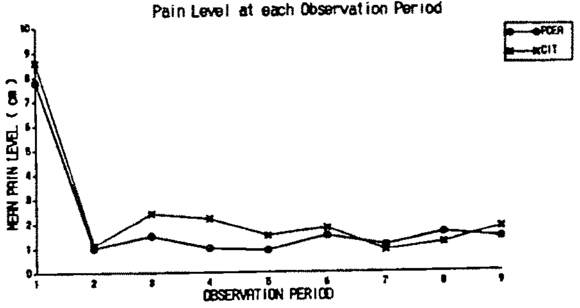

Title: ALERT ANESTHESIA FOR INTRACRANIAL SURGERY

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Removal of brain lesions located near areas of critical function carries a substantial risk of major neurologic deficit. Many advances have contributed toward making this surgery safer, but none quite so much as the technique of alert anesthesia. In using this technique the patient remains awake actively participating in the detailed mapping of areas necessary to critical function by direct intraoperative stimulation of the brain. In this way the patient becomes the primary monitor of neurologic function.

Alert anesthesia was used in 67 craniotomies for arteriovenous malformations or other vascular abnormalities, tumor, or intractable seizures. Each patient was seen in an extended pre-anesthetic visit where all phases of the anesthesia were explained. This conference is particularly important in these patients since intraoperative anxiety attacks can have disastrous consequences. Frequent communication between all members of the team including the patient is critical. All patients in this review were ASA physical status 2 or 3.

Comfort of these patients is of paramount importance since the cases averaged 6 hours in length. Care is taken during positioning to pad all areas of skin with absorbent padding. The patients are kept warm and allowed minor variations in position intraoperatively to maintain comfort. Catheter drainage of urine is used only in females.

Tranquility was accomplished prior to field block using droperidol and fentanyl. These agents were also used throughout the case in amounts considered moderate although seizure patients generally required much larger amounts of these agents. No patient received pre-operative medications on the ward. These were given immediately prior to transport to the operating suite. Usually the neuroleptic agents were used although occasionally diazepam was given and more recently midazolam.

A field block of the scalp was used in conjunction with local infiltration of the planned incision. A weak solution of xylocaine was used to anesthetize the dura. Thiopental was used during the final stages of closure for additional hypnosis as required.

During the mapping of the cerebral cortex both the patient and the anesthesiologist participate by relating the results of stimulation at various points. Due to this direct stimulation the likelihood of a generalized seizure is high. However, only 6 patients had an intraoperative seizure. Of these, 5 occurred during the mapping phase of the procedure and 1 during the opening phase. Being prepared is the key to managing these events. At the beginning of the case methohexital is set out specifically for the control of seizures. Equipment for endotracheal intubation is also available. Of the 6 seizures 5 were short and required no treatment. One required 50 milligrams of methohexital to stop the initial seizure, but continuous seizure activity necessitated early termination of the case. Airway compromise during seizures has not been a problem.

Meticulous blood pressure management is crucial for the control of bleeding especially during surgery on vascular malformations. Awake patients do not tolerate hypotension if induced rapidly or if brought below 70 torr mean. The first symptoms of hypotension are feeling hot and restlessness followed by nausea and vomiting if the hypotension continues. A mean arterial pressure 70 torr was therefore possible during resection in nearly all patients. This was attained using a constant infusion of sodium nitroprusside or trimethaphan as the initial agents of choice. Propranolol supplementation was also used in most patients. Hydralizine was used as an additional drug in about one quarter of the patients. Blood pressure monitoring was done using a radial artery catheter.

Blood loss during alert anesthesia must be closely monitored since excessive blood loss can result in increased anxiety and patient discomfort. Average blood loss during 38 arteriovenous malformation resections was 880 cc with 8 cases having greater than 1 liter of blood loss. This was higher than the 350 cc lost during the other 29 craniotomies.

No complications occurred as a result of alert anesthesia although one patient required intra-operative intubation and two procedures were completed in a second stage due to patient discomfort.

We conclude that alert anesthesia with intra-operative monitoring of speech and motor function has provided an increased margin of safety in the excision of lesions related to major functional areas of the brain.

Title: ISOFLURANE ALTERS THE ABSORPTION KINETICS OF CYCLOSPORINE

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Cyclosporine (Cys) is routinely used for immunosuppression in transplant patients. It is often given orally on call to the operating room so that adequate circulating blood levels are achieved by the time the new organ is implanted. The effect of anesthesia on the pharmacokinetics of Cys has not been previously studied. The aim of this study was to examine the effect of isoflurane anesthesia on the pharmacokinetics of Cys in a rodent model.

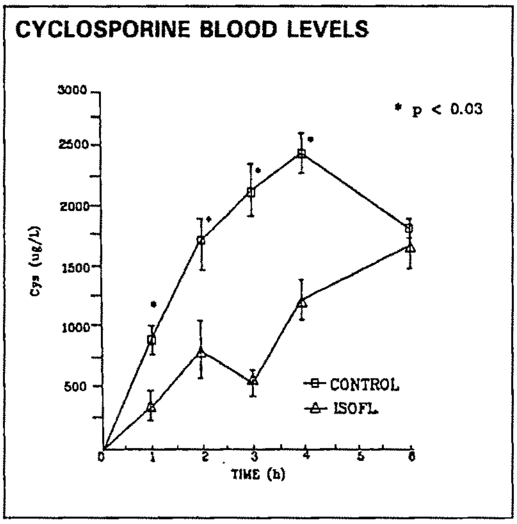
Methods:

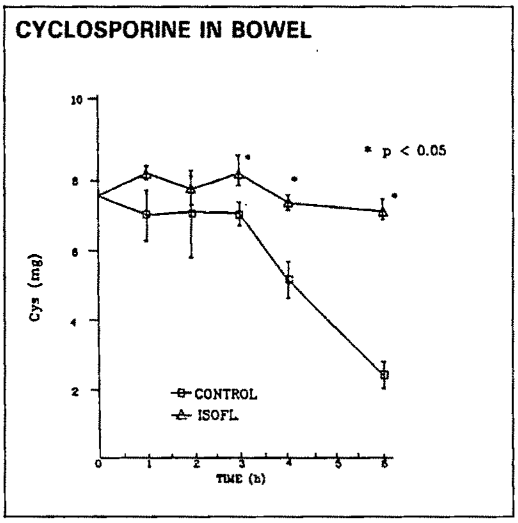
With institutional review board approval, sixty Lewis rats were studied. The animals were weighed, gavaged with Cys 25 mg/kg, and then randomized to received either isoflurane anesthesia (grp Iso n=30) or to serve as non-anesthetized controls (grp Cont n=30). The animals were placed in perspex containers with an orifice at either end which allowed the inflow of 30% oxygen and the outflow of exhaled gas. In the isoflurane group, 1.5% isoflurane was vaporized in the oxygen. The isoflurane concentration was meausred with a Puritan-Bennett infrared gas analyzer. The anethesized animals were placed on a warming blanket to maintain normothermia.

At 1, 2, 3, 4, and 6 hours after the administration of the Cys, five animals from each group were sacrificed by cervical dislocation. Arterial blood for Cys levels was immediately taken. The bowel from the esophagogastric junction to the ileocecal junction was removed, cut into small pieces, and immersed in methanol in order to extract the residual Cys. Cys in whole blood samples and the methanolic bowel extracts were measured by HPLC.

Results:

At all times except six hours, the Cys blood levels were significantly higher in grp Cont (fig.) Conversely, the amount of Cys extracted from the bowel was greater in grp Iso indicating reduced absorption (fig). The peak Cys concentration occurred at 4 hours in grp Cont but in grp Iso peak Cys concentrations were not reached during the study period (6 hrs.)


CYCLOSPORINE BLOOD LEVELS


CYCLOSPORINE IN BOWEL

Conclusion:

We conclude that isoflurane anesthesia significantly reduces the rate of absorption of orally administered Cys. Further investigation will reveal whether this is a non-specific anesthetic effect on gastric emptying or on bowel blood flow. If therapeutic blood levels are required intra-operatively, then this may be best achieved by a continuous intravenous infusion or by administration of the oral dose 3-4 hours pre-operatively.

Title: SPINAL VS GENERAL ANESTHESIA: LONGTERM INTELLECTUAL AND MEMORY EFFECTS IN A GERIATRIC POPULATION

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There still remains controversy about the relative advantages and disadvantages of general anesthesia (GA) and regional analgesia (RA) for major surgery in geriatric patients. One important concern is that GA may result in more impairment of postoperative mental function. The conclusions from previous studies have been limited by the use of unstructured interview techniques[1], a limited number of tests[2], or small sample sizes[3]. The aim of our study was to prospectively compare the longterm effects of GA and RA on intellect and memory in geriatric patients using a sensitive battery of tests.

Methods:

With institutional board approval, patients over the age of 60 years scheduled for elective knee arthroplasty were studied after giving informed consent. They were randomized to receive a GA or RA. The actual choice of drugs was determined by the attending anesthesiologist and all the surgery was performed by one of two orthopaedic surgeons. Patients with psychiatric or neurological illnesses or a limited ability to understand English were excluded. Intra-and post-operative blood pressure, drugs, and fluid administered were carefully recorded.

Psychometric testing was performed the day prior to surgery and again three months later by a psychometrist blinded to the type of anesthesia. Three months was chosen as being long enough post surgery to eliminate the confounding effects of sedative/analgesics and to allow the patient to become fully participant in their activities of daily living. Psychometric testing took 2½-3 hours. The following tests were performed: Wechsler Memory Scale Revised, Wechsler Adult Intelligence Test Revised, Controlled Oral Word Association, Finger Oscilation Test, Two Point Discrimination, Trail Making Test, Sickness Impact Profile, Activities Pattern Indicators.

Statistical analysis used MANOVA and ANOVA as appropriate.

Results:

Seventy-six patients completed the study. An additional 20 failed to return for follow-up. GA patients received thiopental, succinylcholine, isoflurane, N_2O, and fentanyl. The RA group received tetracaine spinals and up to 10 mg diazepam for sedation. There were no statistically significant differences between the groups in terms of intra-operative or post-operative BP, duration of surgery, or the amount of IV fluids given. There were no significant differences between the groups in any of the psychometric tests. The improved scores in both groups at the follow-up visit is consistent with a practice effect.

Conclusions:

We conclude that there is no difference in the longterm intellectual or memory effects of RA or GA in this patient population. The reported cases of longterm post-operative mental deterioration may represent sporadic events, some special local circumstances or, more likely, the effect of some as yet unidentified factor. Our study indicates that the choice of anesthetic is not a major factor when longterm post-operative mental deterioration occurs.

	GENERAL ANESTHESIA		REGIONAL ANESTHESIA	
n	46 M=21	F=25	30 M=12	F=18
AGE (Yrs.)	69.7±6		68.0±5.8	
	PRE	POST	PRE	POST
Verbal Memory	95.1±13.7	100.8±13.9	98.6±17.0	104.0±16.0
Visual Memory	91.4±13.6	93.7±15.0	93.6±16.4	99.5±16.9
Delayed Recall	92.3±11.2	97.9±13.8	95.4±16.7	102.7±18.0
Verbal IQ	95.8±12.8	97.5±12.4	99.5±15.7	101.5±15.4
Performance IQ	95.4±11.3	98.3±11.0	98.6±11.1	102.3±10.6

Mean±SD

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Title: DOSE EFFECT REPONSE OF KETAMINE ON MOTOR EVOKED POTENTIALS (MEP) FOLLOWING TRANSCRANIAL MAGNETIC STIMULATION, IN PRIMATES

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Introduction. Electromyographic response (EMG) recording after transcranial magnetic stimulation (TMS) of the motor cortex is a new clinical tool for testing the descending motor pathways of the nervous system. Magnetic stimulation is preferred over conventional electrical stimulation because the former is electrodeless, painless, and non-injurious (1). Motor evoked potential (MEP) monitoring has been proposed for intraoperative use when the integrity of the motor tract is in jeopardy. The present study demonstrated the dose effect response of ketamine (Kt) when used as anesthetic by means of MEP, following TMS, in primates.

Methods. Ten normal adult cynomolgus monkeys (Macaca Fuscata), weighing 5.5 to 6 Kg, were subjected to noninvasive TMS using a magnetic stimulator (Novametric Magstim-200) producing maximum power of 1.5T (100%). The animals were initially immoblized with Kt 10mg/kg IM and incremental doses of Kt 5mg/kg IV bolus every 15 minutes were given to a total dose of 50mg/kg. The EKG, arterial blood pressure, and rectal temperature were regularly monitored. The magnetic coil was positioned on the scalp unilaterally over the motor area as described in our previous study (2). The EMG responses from the contralateral hypothenar and abductor hallucis muscles were recorded with Grass needle electrodes. A Nicolet Pathfinder II averager was used to record and store the resultant responses following TMS with 100% magnetic intensity (1.5T). Baseline EMG responses were monitored after the initial Kt dose, while the animal was lightly anesthetized, and following each incremental dose of Kt. The threshold of magnetic intensity was also identified after each incremental dose of Kt. The peak latency and peak-to-peak amplitude of the EMG waveform were studied and a one way analysis of variance with repeated measures for Kt dosage was performed on the data.

Results. The MEP responses following TMS were found to be consistent and reproducible in all animals at all different Kt doses (total dose 50mg/kg). All animals were in deep surgical anesthesia after a total Kt dose of 10-15mg/kg, demonstrated with clamp tail test and subcutaneous electrical stimulation. Table 1 shows the peak latencies of EMG responses of the contralateral hypothernar and abductor hallicus muscles after each incremental dose of Kt. The peak latencies were significantly delayed after a total dose $\geq$40mg/kg for the hand and $\geq$35mg/kg for the foot, EMG responses ($p<.05$). Also, there was a significant amplitude depression after total dose $\geq$20mg/kg for the hand and $\geq$15mg/kg for the foot, EMG responses ($p<.05$). However, there was a wide amplitude variability. The baseline threshold of magnetic intensity was 50-60% in all animals, and was unchanged throughout the experiment in 8 of 10 animals. TMS threshold was increased by 10% in two Kt treated animals. No clinical seizure activity was noted in any animal and all animals have remained normal.

Discussion. The authors previously documented the reliability of TMS in eliciting MEP in primates (2). The MEP response was well preserved and reproducible during deep Kt anesthesia (total dose 50mg/kg). Kt had minimal effect on the magnetic intensity threshold. However, there was a significant amplitude depression with Kt total dose $\geq$15mg/kg and latency delay at considerable higher dose $\geq$35-40mg/kg. Bickford et al, used TMS in awake humans, demonstrating that simultaneous electrical scalp stimulation and voluntary muscle contractions can potentiate the TMS-MEP (1). This observation was attributed to neuronal facilitatory effect on MEP. Massopust et al, reported that Kt induced excitatory effects on the extrapyramidal and limbic systems in monkeys with enhancement of the spontaneous electrical activity (3). Kayama and Iwama found Kt potentiation of the evoked potential of the sensorimotor cortex in response to single shock electrical stimulation in cats (4). The present study showed that Kt is an excellent anesthetic agent that can be used whenever intraoperative MEP recording is desired. Although we feel this study is a step towards noninvasive intraoperative MEP utilization; nevertheless, further observations are needed before it is applicable to humans.

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TABLE 1

TOTAL KT DOSE	MEAN PEAK LATENCY (SD) HYPOTHENAR Ms	ABDUCTOR HALLUCIS Ms
10 mg/kg	14.4 (.78)	21.4 (.57)
15 mg/kg	14.9 (.57)	22.3 (1.3)
20 mg/kg	14.5 (1.0)	22.5 (2.6)
25 mg/kg	15.2 (1.6)	22.7 (1.0)
30 mg/kg	15.9 (2.5)	22.6 (1.8)
35 mg/kg	15.5 (2.5)	23.2 (1.0)*
40 mg/kg	16.0 (2.7)$^{+}$	23.3 (1.4)*
45 mg/kg	17.0 (3.3)*	24.1 (1.2)*
50 mg/kg	16.4 (2.7)*	24.2 (1.8)*

$^{+}p<.05$ *$p<.01$

ITCHING AND HERPES SIMPLEX LABIALIS WITH EPIDURAL MORPHINE AFTER CESAREAN SECTION AND HYSTERECTOMY.

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INTRODUCTION

Recent studies (1,2) have shown an increased incidence of itching and Herpes simplex labialis (HS) infections after the administration of epidural morphine for cesarean section(CS). In a previous report (1), we found that pregnant women are prone to these complications (1). In the present study, we evaluated patients undergoing a CS or hysterectomy for the occurrence of HS infections and itching after the administration of epidural morphine for postoperative analgesia. For comparison, we studied patients undergoing CS who received intramuscular (IM) morphine as sole postoperative analgesia.

METHODS

Seventy-six patients were studied over a 6-month period with the approval of the institutional review board. During the 1st, 3rd, and 5th months of the study, 26 patients underwent CS with epidural anesthesia, consisting of an average of 25 ml 2% lidocaine with epinephrine 1/400,000. These patients received 3 to 5 mg of preservative-free morphine epidurally once at the end of the procedure, then up to twice a day as needed for pain, for 2 to 5 days (group A). During the 2nd, 4th, and 6th month, 18 patients underwent the same procedure with the same epidural anesthesia protocol. These patients, however, received 10 mg morphine IM up to twice a day as needed for pain (group B). Thirty-two patients underwent a vaginal or abdominal hysterectomy under general or epidural anesthesia. These patients were given 3 to 5 mg preservative-free morphine epidurally up to twice a day, for 2 to 5 days postoperatively (group C). All patients were evaluated for the first 5 days and on the 9th day postoperatively for the occurrence of itching and HS. When HS infection was present, dermatologic consultation confirmed the diagnosis. Binary probit analysis was used to test overall difference among groups. The Fisher exact test was used to determine statistical differences between individual groups.

RESULTS

The results are summarized in Table I. Probit analysis reveals an overall significant difference among all groups in terms of the occurrence of itching and HS. For itching, a 2 x 2 Fisher exact test revealed groups B and C are significantly different from group A. Itching occurs most often in group A and only after administration of epidural morphine. Group A is statistically different from groups B and C in terms of HS, groups B and C are not statistically different for HS. In group A, all patients who developed HS also had itching. In group C, however, only 1 of 32 patients developed HS, although 15 had itching. HS occurred only in patients who had epidural morphine, while the combination of HS and itching occurred only in group A.

DISCUSSION

In this study, the postoperative occurrence of HS was virtually restricted to group A, with one patient in group C the only exception. The reason is unclear. Speculations include the following. Pregnant women have higher beta-endorphin levels (1). This may explain the higher incidence of itching in group A patients, who may have had a higher total opiate concentration in the brain stem. Itching may trigger HS indirectly by causing mechanical irritation from rubbing and scratching the skin. Direct influence of opiates on the trigeminal tract may also be responsible for HS (1). A contributing factor may be decreased immunologic response during pregnancy (3,4). Pregnant women have a decreased immunity to certain viral and bacterial infections. In our study, pregnant women who received IM morphine after CS (group B) did not develop HS. Only 1 patient in group C developed HS, despite the occurrence of itching in 15. However, these patients represent a different age group and were nonpregnant, which influenced their immunologic status. In addition, higher preexisting beta-endorphin levels and different hormone levels (corticosteroids, progesterone) in group A compared with group C, may have contributed to the observed differences.

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TABLE I: No. of patients with itching and HS

	TOTAL	ITCHING	HS
Group A	26	21	9
Group B	20	0	0
Group C	32	15	1

Binary probit analysis: Itching x^2 (2) = 37.95; $p < .0001$; HS x^2 (2) = 17.29; $p < .0001$
Fisher exact test: Itching: A vs B, $p < .00001$; A vs C – $p = .0066$; B vs C, $p = .00012$; HS: A vs B, $p = .0028$; A vs C, $p = .00192$; B vs C, $p = .6154$

Statistical Analysis by Dr. T. Rudy, M.D.

Title: SYSTEMIC ABSORPTION OF LIDOCAINE DOES NOT CONTRIBUTE TO TREMOR DURING EPIDURAL ANESTHESIA

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Introduction. Tremor, shivering, or uncontrollable shaking often occurs in patients who receive epidural anesthesia, and is seen frequently in pregnant patients undergoing cesarean section with epidural lidocaine anesthesia (1). The etiology of this tremor is frequently assumed to be thermoregulatory shivering in response to skin surface cooling, cold intravenous fluids, or stimulation of spinal thermoreceptors (2). However, the tremor is not related to core temperature (1), and patients with tremor rarely complain of feeling cold. Tremor during recovery from general anesthesia resembles clonus, not thermoregulatory shivering, and occurs at endtidal isoflurane concentrations between 0.1-0.2% (3). This tremor is thought to result from anesthetic-induced spinal disinhibition. Systemic absorption of epidural lidocaine produces sedation; this anesthetic effect may also cause spinal disinhibition similar to that of low dose isoflurane. Therefore, we studied the contribution of intravenous lidocaine to the development of tremor and plantar-flexion induced clonus (as a sensitive indicator of spinal disinhibition) in a double-blind placebo cross-over study.

Methods. After approval by our clinical investigation committee, informed consent was obtained from five healthy male volunteers. All subjects were studied in a warm room to prevent thermoregulatory shivering. Subjects were studied on two different days. On one day the subject was given intravenous lidocaine (bolus dose of 1 mg/kg followed by an infusion of 50 µg/kg/hr for 30 minutes, followed by an additional 0.5 mg/kg bolus and an infusion of 75 µg/kg/hr for 30 minutes); on the other day the subject received a saline infusion. The order of infusions was determined randomly in a double-blind fashion. The following measurements were made every 5 minutes during the infusions: tympanic membrane (core) and average skin surface temperatures (4), plasma lidocaine levels, and the presence of spontaneous tremor and plantar flexion-induced clonus in both legs. Central thermoregulatory vasoconstriction was assessed using skin temperature gradients (forearm temperature minus index finger temperature) (5). One leg was alternately cooled to 28°C and then rewarmed to control temperature with water blankets during each infusion period to assess the contribution of local skin cooling to the development of tremor and/or clonus. The data was analyzed using Chi-square with $P<0.05$ considered significant.

Results. The mean (± S.D.) age, height, and weight of the subjects were as follows: 22±4.1 years, 158±4.8 cm, and 76.7±6.0 kg. Room temperature was greater than 24°C in all study periods, thus maintaining normal core temperatures and average skin temperatures greater than 33°C. No subject demonstrated significant peripheral vasoconstriction. Lidocaine levels were 2.2±1.0 µg/ml (mean±S.D.) during the low dose infusion, and 3.4±1.4 µg/ml during the high dose infusion. Spontaneous tremor was never observed during the study. Clonus (2-4 beats, never sustained) was elicited in only 5 of the 60 epochs of lidocaine infusion, and in 1 of 60 epochs of saline infusion. This incidence of clonus was not different between lidocaine and saline infusions. Clonus occurred equally in the warm and the cool extremities.

Discussion. We observed no tremor and only occasional clonus in volunteers with serum lidocaine levels similar to those seen during epidural anesthesia. Therefore, it is unlikely that systemic absorption of lidocaine is the primary etiology of tremor during epidural anesthesia. It remains possible that systemic absorption of lidocaine combined with other factors, such as pregnancy, produces tremor. Alternatively, the observed tremor may, in fact, be thermoregulatory shivering.

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Title: DIAPHRAGMATIC RECOVERY FROM ATRACURIUM AS MEASURED BY SINGLE TWITCH, LENGTH CHANGES AND FORCE-FREQUENCY CURVES.

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Introduction. Diaphragmatic recovery from paralysis following vecuronium and atracurium was measured by the force developed by single twitch (ST) phrenic nerve stimulation, which reached 75% of control in 15 minutes[1,2]. Since both onset and recovery of diaphragmatic paralysis might be faster if measured via ST as compared to tetanic stimulation, we measured direct *in-vivo* force-frequency curves and ST of the dog's diaphragm during recovery from atracurium together with limb muscle ST stimulation.

Methods. Six mongrel dogs anesthetized with 30 mg/kg of pentobarbital were intubated and breathed spontaneously. Diaphragmatic length was measured by sonomicrometer transducers (Triton Technology, San Diego) which consist of piezo electric ceramics, 2 mm in diameter, capable of emitting a high frequency burst of ultrasound when electrically stimulated. Upon reaching a second transducer, the ultrasound waves induce a voltage. Time of propagation of the ultrasound between both transducers is proportional to distance. One pair of transducers was implanted both in the costal (cos) and crural (cru) diaphragm via laparotomy. Maximal shortening of costal and crural segments were measured as percent of resting length at FRC (%LFRC). Abdominal pressure was subtracted from the pleural pressure to give transdiaphragmatic pressure (Pdi). Bilateral phrenic nerve roots were stimulated in the neck. Force (ΔPdi) and %LFRC were measured during supramaximal phrenic stimulations at 5, 10, 20, 50 and 100 Hz before (control) and after injection of atracurium (0.2 mg/kg) when tidal volume (VT) was 30% of control (VT30). Ventilation was then controlled until spontaneous VT was again VT30 and all measurements repeated at regular intervals (recovery). Before each set of force-frequency curves, supramaximal twitches were simultaneously applied to the diaphragm and to a limb muscle attached to a force-displacement transducer.

Results. The average recovery of diaphragmatic and limb muscle ST height was 90% in 30 minutes. Maximum Δ Pdi and %LFRC were reduced by atracurium to 40-50% of control at VT30. Recovery times of Δ Pdi and %LFRC at peak values after atracurium were expressed as percent of ST recovery time. (table 1) Contractile properties (between 20 Hz - 100 Hz) and Pdi recovered considerably slower than ST. There were no significant differences between cos and cru maximum shortening. Average Δ Pdi and %LFRC after 60 min. of atracurium injection were still below 70% of control. High-frequency (50-100 Hz) Δ Pdi and %LFRC were almost systematically below those values obtained at low-frequency (5-10-20 Hz) of stimulation (table 2).

Discussion. Diaphragmatic contractility was not accurately reflected by ST during neuromuscular blockade[3] and after fatigue[4], in which recovery measured by ST seems faster than that of tetanic stimulation. In fact, this study did show a faster pattern of recovery of the ST in both the diaphragm and the limb muscle while force-frequency curves showed a reduced Δ Pdi and contractility at both costal and crural diaphragmatic segments. Slow recovery and force failure at high-frequencies of stimulation may be the result of reduced transmission at the neuromuscular junction or failure of propagation in the muscle fiber membrane. During recovery from muscle relaxants (as opposed to fatigue) there is a persistent reduction in diaphragm force and maximum shortening at high-frequencies of stimulation.

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Table 1

Time of peak recovery (in percent of ST recovery)

	5 Hz	10 Hz	20 Hz	50 Hz	100 Hz
ΔPdi	146 ±23	149 ±13	127 ±17	141 ±21	145 ±19
%LFRC cos	86 ±12	96 ±16	116 ±19	126 ±22	147 ±23
%LFRC cru	80 ±30	82 ±12	114 ±15	147 ±23	147 ±23

mean ± SEM

Table 2

Time course of ΔPdi and %LFRC (in percent of control)

	time (min)	Low-frequency	High-frequency
ΔPdi	0-15	30 ± 4	23 ± 4
	15-30	47 ± 6	55 ± 6
	30-45	53 ± 6	39 ± 6
	45-60	55 ± 6	56 ± 6
%LFRC cos	0-15	33 ± 5	28 ± 4
	15-30	57 ± 5	47 ± 5
	30-45	70 ± 6	48 ± 5
	45-60	61 ± 8	70 ± 3
%LFRC cru	0-15	33 ± 6	26 ± 4
	15-30	57 ± 6	45 ± 5
	30-45	72 ± 7	38 ± 5
	45-60	66 ± 8	65 ± 4

mean ± SEM

Title: LOW-DOSE INTRATHECAL MORPHINE FOR POSTOPERATIVE ANALGESIA IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION OF THE PROSTATE

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Introduction. Morphine Sulfate (MSO4), when injected intrathecally (IT) in combination with a local anesthetic to produce a subarachnoid block, has been shown to be highly effective in providing postoperative analgesia for patients undergoing transurethral resection of the prostate (TURP)[1,2]. However, significant side effects accompany the relatively high dose (1 mg) employed in these studies. We investigated the analgesic efficacy, and evaluated the side effects of low-dose IT MSO4 (0.1 and 0.2 mg) for TURP.

Methods. Following approval of the Human Subjects Committee, 30 ASA class II and III patients scheduled to undergo TURP were asked to participate in our study. The evening prior to surgery, written informed consent was obtained and the patient was instructed in the use of an Inverse Numerical Visual pain scale. All patients were premedicated with diazepam 2.5 mg po at 0600, and received lidocaine 5%, 75 mg in dextrose 7.5% IT as their primary anesthetic. Patients were randomly assigned to one of three groups: Group 0 served as control and received no IT MSO4; Group 1 received preservative-free MSO4 (Duramorph) 0.1 mg IT; Group 2 received MSO4 0.2 mg. The final volume of each injectate was adjusted to 1.7 ml with saline, as necessary, by a separate individual to maintain a double-blind protocol.

Pain severity, analgesic requirement, and the presence of side effects (respiratory rate ≤ 8, pruritus, drowsiness, nausea, or vomiting) were scored 6 times for each patient: at 3, 5, and 7 hours post-op; post-op day (POD) #1 am and pm; POD #2 am. All patients were admitted to the surgical ICU overnight for monitoring. Post-op pain scores as a function of peak anesthetic dermatomal level, and as a function of duration of surgery, were examined by linear regression. Group-mean pain scores were evaluated by t-tests. The intergroup incidence of side effects was examined by chi-square analysis. Height, weight, age, and duration of surgery were compared by analysis of variance. Level of anesthesia was analyzed by Wilcoxon's Rank-Sum test. In all cases $p<0.05$ was considered to be significant.

Results. Mean group weight, duration of surgery, age, and level of anesthesia did not differ. Group 2 patients were significantly shorter than Group 0 (difference of the means 6.9 cm). There was no association between the duration of surgery and the total pain scores for any of the groups; nor was their an association between level of anesthesia and pain scores.

Pain scores and number of analgesic interventions 3 hours post-op were not significantly different. From 5 hours post-op until the end of the study period, Group 0 had significantly more pain and required more analgesic interventions than Groups I or II. Groups I and II did not differ in overall pain scores, or average analgesic requirements.

While there were two patients in Group I that had pruritus, there was no association between morphine administration and the development of pruritus. Three patients in Group II were treated with up to 0.3 mg of naloxone for nausea/vomiting (n/v). Group II patients had significantly more n/v than Group 0.

All patients had adequate surgical anesthesia. No patients had respiratory depression. There was no difference in the degree of drowsiness between groups. Three patients who were in Groups I & II received supplemental oral analgesics on POD #1 pm, or POD #2. Five patients in Groups I & II who experienced no or minimal pain, received belladonna & opium suppositories (b&o), for bleeding presumably due to bladder spasm. All patients in Group 0 required analgesics. All patients in Groups I & II were "satisfied" with their post-op analgesia; 4 of 10 patients in group 0 were not satisfied despite receiving some combination of b&o, Percoset, Tylenol #3, and MSO4 IV.

Discussion. In this group of patients, IT MSO4 was highly effective in providing post-op analgesia after TURP. No episodes of respiratory depression occurred. MSO4 0.2 mg was associated with a higher incidence of n/v, and the quality of analgesia was not different between patients who received 0.1 or 0.2 mg of MSO4. Therefore, we recommend that 0.1 mg of MSO4 be used.

We thank David A. Young, M.S. for performance of the statistical analysis.

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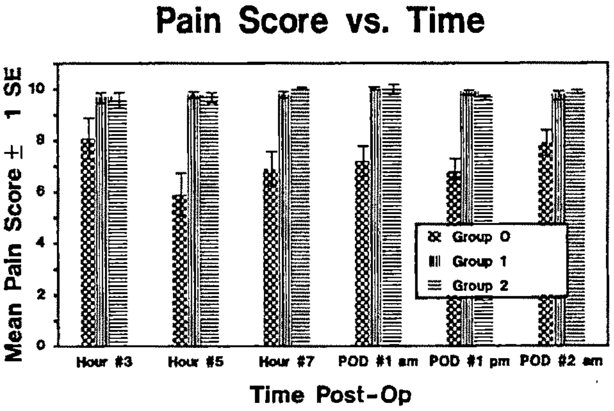

PAIN SCORED ON AN INVERSE NUMERICAL VISUAL SCALE.
10 = "NO PAIN"; 1 = "WORST PAIN EVER".

Title: **AUTOMATED EEG ANALYSIS DURING RECOVERY FROM ISOFLURANE ANESTHESIA IN PEDIATRICS.**

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__Introduction__. Following an inhalational anesthetic, the anesthesiologists' concern foccusses on the prompt return of protective reflexes and the recovery of consciousness. Processed EEG is acknowledged to be a useful parameter of anesthetic depth, however, its validity as an index of recovery from anesthesia has not been yet consistently established. Isoflurane, on the basis of its low blood/gas solubility coefficient and minimal metabolism, should theoretically result in reversible brain effects which parallel the return of normal consciousness level. To confirm this hypothesis, a study was designed to examine the EEG power spectrum pattern and its relationships with clinical indicators of wakefullness in a group of children emerging from isoflurane anesthesia.

__Methods__. Following institutional approval and parent's informed consent, twelve patients (age 4.4 years ± 4 SD; range 4 mo.-12 years), ASA physical status I or II, scheduled for elective minor surgery were studied. Premedication consisted of meperidine, promethazine and atropine IM. Anesthesia was induced by mask with a gas mixture of N_2O/O_2 (60/40%) and isoflurane. Tracheal intubation was facilitated with succinylcholine and maintenance of anesthesia was accomplished with isoflurane (0.8-2%) and N_2O (60% in O_2). Ventilation was either spontaneous or assisted. Two channels of EEG were processed in real time before (control) and after anesthesia (Post-A) by a computer system (Cerebro-Trac, Neuroscience) which is based upon the fast Fourier tranform method. Trended spectral edge frequency (SEF), defined as the highest significant frequency in the current power spectrum, and the total EEG amplitude (AMP) were sampled at 2 minute intervals from both hemispheres (RH and LH). Time course of SEF and AMP during recovery from anesthesia was analyzed with a non-linear regression. Response to a simple command and/or persistent spontaneous eye opening were interpreted as signs of wakefulness and computed as awake time. Automatic non invasive blood pressure, capillary blood gas analysis and ECG were monitored.

__Results__. SEF and AMP were collected during 95 min ± 29 SD after isoflurane anesthesia (Table 1). Differences between hemispheres were not significant. Full recovery time for SEF (30 min ± 20 SD) and AMP (34 min ± 21SD) were not significantly different from awake time (31 ± 64 min). A significant relationship was found between AMP recovery time and awake time (fig. 1). SEF recovery time correlated with anesthesia duration ($p < 0.05$). AMP between 0 and 50% of awake time was significantly lower than control ($p<0.03$). During the post-A period diastolic blood presure increased from 63 torr ± 12 to 69 torr ± 52SD ($p<0.03$). Before discharge from recovery room, capillary blood gases breathing room air were: pH=7.35 ± 0.05; PCO_2 = 39 torr ± 4; PO_2 = 67 torr ±7; SaO_2% = 92 ± 2 and BE =-3 ± 2.

__Discussion__. Progressive recovery of AMP probably depends on the rate of fall of alveolar concentration of the agent. Time course of SEF showed spontaneous paradoxical EEG arousal (increased syncronization and return to slow activity) only in six patients, in contrast to higher incidence reported in adult volunteers[1]. In conclusion, this study suggest a close relationship between wakefulness indicators and EEG normalization. Baseline return of EEG pattern after isoflurane anesthesia validates clinical discharge criteria for pediatric outpatient anesthesia.

__References__.

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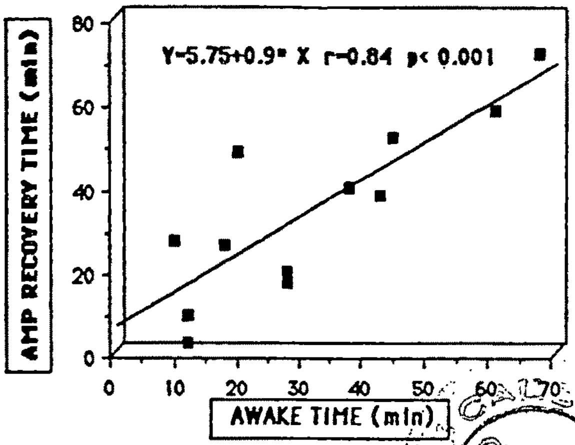
__Table 1__

	Control		Post-A	
	RH	LH	RH	LH
SEF Hz	11.8 ± 5	12.3 ± 6	9.8 ± 15	10.0 ± 16
AMP μV	36.0 ± 9	37.8 ± 10	27.6* ± 30	28.4* ± 20

mean ± SD, *$p < 0.01$ from control.

Fig. 1



Title: **AN EVALUATION OF TWO RAPID NON-INVASIVE BLOOD PRESSURE METHODS DURING GENERAL ANESTHESIA INDUCTION**

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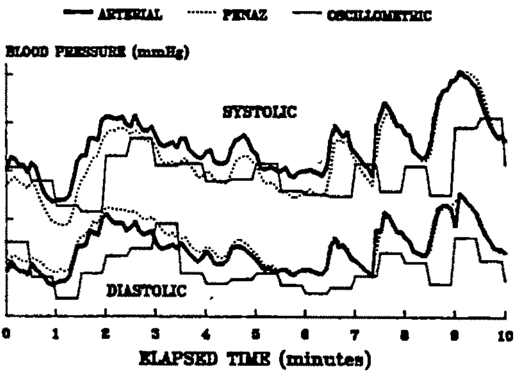
Introduction: Non-invasive oscillometric blood pressure monitors, introduced into clinical practice in the 1970's, have been universally accepted and commonly used throughout the USA. The instruments have been consistently improved since their introduction, and the latest models incorporate an internal cuff air reservoir, enabling a "stat" mode, with real-time pressure readings at least every 30 seconds. A second method, the Penaz technique, has become clinically available very recently. We compared and evaluated each of these methods simultaneously during anesthetic induction.

Methods: The CRITIKON^{R} Dinamap^{R} Model 1846SX was selected as representative of the latest oscillometric technology (OSC), to be compared with the OHMEDA^{R} Finapres^{R} Model 2300, the only available Penaz device (PEN). Digital blood pressure from a radial intra-arterial catheter (IAC) connected to a SPACELABS^{R} Model 511 invasive monitor was used as the standard (IAC). Following approval of the Institutional Review Committee, 25 patients scheduled for general surgical procedures requiring general anesthesia and invasive blood pressure monitoring were selected for the study after informed consent was obtained. Patients with known severe vascular disease were excluded. The IAC was statically and dynamically calibrated and tested[1], and an adjustable damping device was installed if indicated. Baseline oscillometric blood pressure was determined in each arm to eliminate anatomical inaccuracy. The PEN was placed on the middle finger ipsilateral to the IAC, with the OSC cuff on the contralateral arm, both in accordance with manufacturer's instructions. Automated serial data collection via the Duke DATAQ system enabled real-time digital data to be automatically recorded every 5 seconds during the first 10 minutes of general anesthesia. A typical case record is shown in the figure below. Data points reflecting obvious artifact errors were deleted for each device and data were analyzed for precision and bias of each instrument in accordance with reference 2.

Results: PEN was superior to OSC for systolic, diastolic, and mean pressure parameters. The table below lists the frequency with which each monitor performed better than the other with 95% confidence. The last 2 columns show the average precision for each monitor. Both monitors showed a bias toward underestimation of intra-arterial blood pressure.



	Better Performance (%)		Precision (mmHg)	
	PEN	OSC	PEN	OSC
Systolic	46	27	17	19
Diastolic	60	27	9	10
Mean	53	13	9	11

Discussion: Both monitors were able to track blood pressure trends well. Even in "stat mode", the effective OSC sampling interval was approximately 30 seconds. PEN methodology, with its beat-to-beat output, was therefore faster in relative ability to predict changes in hemodynamics. The delay in readings by OSC appears to be the prime reason for its lower accuracy in real time. We conclude that PEN is more valuable for rapid tracking of blood pressure changes on anesthetic induction.

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Title: DIAZEPAM VS. MIDAZOLAM IN THE PREVENTION OF LIDOCAINE TOXICITY IN RATS

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Introduction. It has previously been demonstrated that the benzodiazepines protect animals against the central nervous system toxicity of local anesthetics (1). Diazepam has been advocated both to prevent and treat this toxicity (2,3). However, the water insolubility of this drug makes it difficult to obtain reliable blood levels after intramuscular injection (4). When dissolved in propylene glycol it may be used intravenously, but is painful. Midazolam, a water-soluble benzodiazepine effectively produces reliable blood levels when injected intramuscularly and thus may solve the problems associated with diazepam. We have attempted to define whether midazolam is more effective than diazepam in limiting the morbidity and mortality of the local anesthetic, lidocaine.

Methods. The protocol for this study was approved by the Animal Investigation Committee of the University. After determining that the minimum concentration of lidocaine necessary to produce convulsions reliably in our rats was 150mg/kg, 30 male Sprague-Dawley rats (360-430gm, mean 395 gm) were assigned to each of six different groups. Group 1 received lidocaine 150mg/kg intraperitoneally. Group 2 received lidocaine 300 mg/kg i.p. Group 3 midazolam 0.25 mg/kg i.p. followed 15 minutes later by lidocaine 150 mg/kg. Group 4 diazepam 1mg/kg and then lidocaine 150mg/kg. Group 5 midazolam 0.25mg/kg and lidocaine 300 mg/kg. Group 6 diazepam 1mg/kg and lidocaine 300mg/kg. The drugs were commercially available preparations, freshly diluted with normal saline each day. The studies were always performed early in the day, between 8:00 a.m. and 1:00 p.m. All rats were observed for at least two hours, and the development of seizures, and mortality noted. Differences between groups were tested for significance with the Fisher exact test, one tail with $P < 0.05$ considered signficant.

RESULTS (n=30, each group)

	No. of Rats	
Group	Seizures	Deaths
1	12	4
2	24	23
3	8	10
4	1	6
5	15	16
6	1	7

With 150mg/kg lidocaine, both diazepam and midazolam actually increased mortality, while diazepam protected against seizures ($p < 0.003$) and midazolam did not ($p < 0.20$). At 300mg/kg diazepam protected against death ($p < 0.00001$) and seizures ($p < 0.00001$) while midazolam protected against seizures ($p < 0.015$), but not against death ($p < 0.052$). Diazepam was superior to midazolam in preventing seizures at 150mg/kg ($p < 0.0011$), seizures at 300mg/kg ($p < 0.0001$) and deaths at 300mg/kg ($p < 0.016$). Neither drug completely eliminated seizures, nor provided complete protection against death.

Discussion. Midazolam is considered to be approximately four times as potent as diazepam. While the water solubility and the consequent ease of use, coupled with more reliable and predictable blood levels make midazolam theoretically superior to diazepam, these theoretical advantages were not sufficient to demonstrate superiority over diazepam. While midazolam did reduce the incidence of seizures at both 150mg/kg and 300mg/kg lidocaine, the 26.7% (150mg/kg lidocaine) and 50% (300mg/kg lidocaine) incidences are unacceptably high, and in sharp contrast with the 3.3% incidence at both doses with diazepam. The increased mortality at low dose lidocaine was not due to increased convulsions, but appears to be due rather to an additive respiratory depressant effect of the local anesthetic and the benzodiazepine.

Conclusion. Diazepam is more effective and reliable then midazolam in decreasing lidocaine-induced morbidity and mortality in rats.

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Title: PROLONGED MIVACURIUM INFUSION IN CHILDREN

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Introduction: Mivacurium Chloride (BW 1090U) is a short-acting competitive neuromuscular blocking agent, which has been shown to be efficacious and safe in adults and children (1-3). The short duration of action and absence of both tachyphylaxis and phase II block make it suitable for administration by continous infusion as demonstrated in short surgical procedures in children (2). Presently, we evaluated the continous infusion for prolonged surgical procedures (more than 2 h) in children anesthetized with halothane.

Methods: Eight children (ASA status I, 2-11 years) were evaluated. The study was approved by the Subcommittee on Human Studies, Committee on Research of our institution. Parental written consent was obtained. None of the children were receiving antihistaminics or aminoglycoside antibiotics. Premedication was with rectal methohexital (25-30 mg/kg). Patients were anesthetized and maintained at 1% halothane (inspired) concentrations. Precordial heart sounds, blood pressure, EKG, pulse oximeter, end-tidal CO_2 were monitored.

The force of contraction of the adductor of the thumb was recorded on a polygraph by a Grass FT-03 force displacement transducer. The ulnar nerve was stimulated with surface electrodes at the wrist with repetitive train-of-four supramaximal stimuli (2Hz for 2 sec every 10 sec.). The degree of neuromuscular blockade was calculated as percent of control of the first response of the train-of-four (T1).

The children were endotracheally intubated following bolus doses (0.09-0.2 mg/kg) of mivacurium. After recovery from the initial bolus dose, a second bolus dose (0.1 mg/kg) was administered. Once the patient started to recover from the second dose, a mivacurium infusion was started. The mivacurium infusion was prepared by adding 60 mg (30 ml) of mivacurium to 210 ml of 5% dextrose in water, to obtain a mivacurium concentration of 250 ug/ml. The infusion was administered via an I-Med infusion pump at an initial rate of 10 ug.kg-1.min-1. The rate was subsequently adjusted to maintain 90-99% neuromuscular blockade. The infusion rate and the percentage block were calculated at 3 min. intervals. All data are presented as mean ± SE, and a Student's t-test was used for statistical analysis. Data were considered significant if $P<0.05$.

Results:
At the beginning of the mivacurium infusion, frequent adjustments of the rate were needed to optimize maintainance of neuromuscular blockade in the desired range (90-99%). Infusion rates became relatively constant after an initial adjustment period of about 15 min. The data are presented after this initial unstable infusion period. In six of the eight patients studied the surgical procedure lasted for more than 3 hrs. In the other two, the procedure ended two hours following the start of the infusion.

Table 1

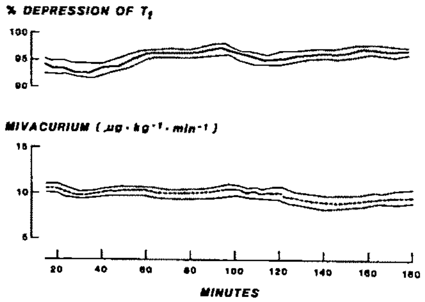
Infusion Period	Infusion Rate ug.kg-1.min-1	% Depression of T1
15-60 min n=8	10.2±0.8 min	94.4±1.5%
63-120 min n=8	10.2±0.7 min	96.7±0.6%
123-180 min n=6	9.4±0.8 min	96.8±2.1%

The mean ± SE (range 6-15 ug.kg-1.min-1) infusion rate to maintain 90-99% neuromuscular depression and the resultant neuromuscular response are summarized in Table 1.

There was no significant difference between the infusion requirements and the % depression of the twitch response in any of the time periods evaluated. For practical purposes after the initial stabilization period very few adjustments were needed. Fig. 1 demonstrates the stability of the mean infusion requirements in the 3 hour infusion period. The slight (NS) change after the second hour is due to the termination of the surgical procedure in one of the children that was requiring relatively high infusion rates (14 ug.kg-1.min-1).

At the end of the surgical procedures, four of these patients recovered spontaneously from the effect of mivacurium. In these patients, the twitch response recovered to 90% of control in 14.5 ± 5.1 min. In the other four patients, the effect of mivacurium was antagonized by atropine 0.03 mg/kg and edrophonium 0.3 mg/kg, recovering to 90% in 11.5± 5.1 min.

Figure 1



Discussion: The constant infusion requirement of mivacurium indicate that it is a non-cumulative drug even when administered continuously for up to three hours. This prolonged infusion did not affect the recovery from mivacurium spontaneously or by the administration of edrophonium. The recovery periods observed after these prolonged infusions were rather similar to those observed after 1-3 bolus doses of mivacurium. It is also important to note that the requirement remained constant despite the presence of halothane. Although some potentiation of neuromuscular effects of mivacurium has been noted with halothane (2), this effect seems to occur in the initial period and does not increase with time at clinical concentrations of halothane. The stability of infusion requirement seems to be one of the major advantages of mivacurium.

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Title: A COMPARISON OF THE WORK OF BREATHING DURING PRESSURE SUPPORT VS ASSIST CONTROL VENTILATION

Authors: MR Graham, M.D., L Blanch, M.D., S Gottfried, M.D., P Goldberg, M.D., J Ramsay, M.D.

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Introduction Ventilated patients breathing in the 'assist' (AC) mode, perform considerable work during inspiration due to mismatching of delivered flow to patient demand and the added work of the external circuit[1]. Pressure support ventilation (PSV) can decrease patient work[2] and overcome external work imposed by the circuit[3]. This suggests that patients may perform less work for a given tidal volume with PSV compared to AC ventilation. The present study therefore, compares the inspiratory work of breathing with these two modes.

Methods: The study was approved by the hospital ethics committee and informed consent was obtained. Five patients, free of pulmonary disease and ready to be weaned from mechanical ventilation post coronary artery bypass surgery were studied. Heart rate, blood pressure, pulmonary artery pressure and oxygen saturation were monitored constantly. Airway pressure (Paw), tidal volume (Vt) (integrated from the inspiratory flow signal) and end tidal CO_2 ($ETCO_2$) were measured at the mouth and recorded continuously. Total inspiratory work across the respiratory system was determined by the integral of Paw vs V_t during PSV, pressure control ventilation (PCV), AC and controlled ventilation (CV) using a Siemans 900-C servoventilator. The ventilatory pattern was matched for Vt, inspiratory time and respiratory rate during each mode and $ETCO_2$ was maintained in the normal range. The difference in total work during controlled breaths (PCV and CV) and the corresponding patient triggered breaths (PSV and AC) represents work done by the patient. Total work for each mode was compared by ANOVA and differences compared by the Student-Newman-Kuhl test, with significance accepted at the $P < .05$ level.

Results: All patients maintained normal hemodynamic, oxygen saturation and $ETCO_2$ values throughout the duration of the study. Figure 1 shows the total inspiratory work (machine work plus patient work) during each mode of ventilation. Each point represents an individual patient and average values are represented by the open symbols and dotted line. Total inspiratory work during PSV was 0.85 ± .16 joules/breath (mean ± SD); it increased to 1.04 ± .18 joules during PCV and to 0.94 ± .15 joules during CV. Inspiratory work during AV was 0.66 ± .18 joules, significantly lower than during all other modes ($p < .05$). Patient work during PSV (PCV-PSV) was 0.186 ± .092 joules/breaths, less than that found during AC (0.276 ± .093).

Discussion The reduction in patient work during PSV is clearly dependent on the level of PSV chosen[2]. We chose a level of PS at which the patient breathed at a rate of 20 breaths/min and maintained $ETCO_2$ in the normal range. At this clinically relevant level of PSV, the inspiratory work of breathing was less than comparable breaths during AC. The reduction in inspiratory work during this mode of ventilation suggests that the decelerating flow pattern and high initial flow in PSV may be more effective in overcoming spontaneous patient efforts than the constant flow pattern of AC ventilation.

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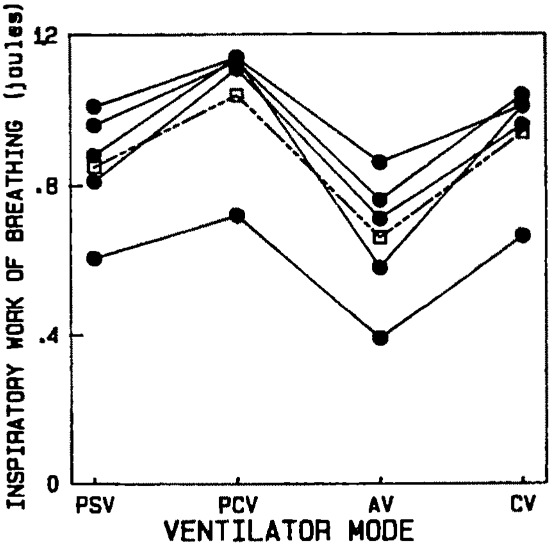

TITLE: THE EFFECT OF A PRIMING DOSE OF VECURONIUM ON SUFENTANIL INDUCED RIGIDITY
AUTHORS: I GRATZ, D.O., GE LARIJANI, PHARM.D., L BOXER, B.A., E VALVANO, R.N. B.S.N., A JACOBI, M.D.
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Introduction: A high incidence of chest wall rigidity has been documented with the use of sufentanil in coronary artery bypass grafting surgery (CABG).[1] The occurrence of rigidity can interfere with positive pressure ventilation and lead to bradycardia, hypoxia and death. At present, the only dependable treatment for the rigidity is the use of paralyzing doses of muscle relaxants. The aim of our study was to evaluate the effect of a priming dose of vecuronium on the occurrence of rigidity produced by a sufentanil induction.

Methods: Following approval by the Committee for the Protection of Human Subjects, twenty ASA II-III patients (5F, 15M) scheduled to undergo elective CABG gave informed consent to participate in this study. Patients were excluded from the study if they had: chest pain within 24 hours prior to surgery; an ejection fraction < 30%; central nervous system or neuromuscular diseases; required an intraaortic balloon pump and; been hemodynamically unstable. Patients were alternately placed into a control group (A) [N=10, 3F, 7M] or an experimental group (B) [N=10, 2F, 8M]. Patients in group A [61 (± 14) years old] were given saline while group B patients[63 (± 13) years old] were pretreated with 0.01 mg/kg of vecuronium 5 minutes prior to sufentanil infusion. All patients were premedicated with morphine (0.1 mg/kg, IM) and scopolamine (0.43 mg, IM) 90 minutes prior to induction. In both groups, anesthesia was induced with sufentanil (0.01 mg/kg) at a rate of 1 mg/kg/min. A continuous electromyogram (EMG) using four 27-gauge teflon coated monopolar needle electrodes were placed into the following muscle groups: sternocleidomastoid (SCM), rectus abdominus (RA), ninth intercostal (I) and gastrocnemius (G). The electrode placement was confirmed by a brief burst of insertional activity. Intra-operatively, patients were monitored by BP cuff, radial artery cannulation, thermodilution pulmonary artery catheter, and pulse oximeter. Cardiac output was measured in triplicate. Clinical signs of severe rigidity were evaluated by the individual maintaining the airway. This was defined when mask ventilation was inadequate after the insertion of the airway. When evidence of rigidity was encountered and ventilation proved difficult, patients in group A received succinylcholine (1.5 mg/kg) while patients in group B were given 0.15 mg/kg of vecuronium IV. In all patients, intermittent positive pressure (IPP) ventilation was given for 45 to 60 seconds prior to intubation. Muscle activity was continuously recorded during induction and was rated on a 0 to 5 scale, where 0 presents no EMG activity and 5 presents full interference pattern. Data was analyzed using one and two-way ANOVA and is presented as mean (SD). A $P < 0.05$ was considered significant.

Results: There was no significant difference in the demographic variables between the two groups. All 20 patients manifested clinical signs of severe rigidity. However, clinical signs of rigidity were manifested at a significantly later time in patients pretreated with vecuronium [5(1) min vs. 7.6(2) min, $P < 0.05$]. No significant difference was demonstrated between the two groups with respect to maximal activity measured by EMG or time to attain maximal activity in the muscles studied. There was no significant difference in the systolic blood pressure, diastolic blood pressure, heart rate or cardiac output prior to induction of anesthesia between the two groups. These hemodynamic variables did not change significantly after induction of anesthesia, at the time of clinical signs of severe rigidity and at one, two and three minutes after the administration of muscle relaxants in either group. Arterial pH, pCO_2, PAO_2 or base excess did not change significantly over the time course of the study in these patients. Furthermore, once the rigidity was treated with either succinylcholine or vecuronium, it did not occur again.

Discussion: There is a high incidence of chest wall rigidity following narcotic induction of anesthesia.[2] The incidence of chest wall rigidity in our study was 100%. Pretreatment with intubating doses of muscle relaxant prevents the occurrence of severe chest wall rigidity. The results of this study demonstrated that pretreatment with priming dose of vecuronium does not effect the incidence of rigidity. It did significantly delay the onset of chest wall rigidity thereby allowing a larger dose of sufentanil to be administered. This may allow an anesthetic dose of sufentanil to be given before rigidity manifests itself. Twenty percent of the patients were unable to tolerate this priming dose and complained of difficulty breathing requiring intervention. No significant association was observed between the EMG changes in the muscles studied and the clinical manifestations of rigidity. Furthermore, we did not observe any change in pH or base excess in either group of patients as a consequence of rigidity.

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TITLE: MEASURING SVR IN PATIENTS WITH AND WITHOUT PERIPHERAL VASCULAR DISEASE BY NONINVASIVELY RECORDED WAVEFORMS (FINAPRES)

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INTRODUCTION: The key to optimal intraoperative management of cardiac function is the ability to detect changes in hemodynamics instantaneously. The Finapres utilizes the unloaded artery principle of operation. It measures beat-to-beat blood pressure using a small finger cuff that contains a photoplethysmographic volume transducer and an inflatable air bladder. The aim of this study was to (1) compare the accuracy and precision of the Finapres in comparison to an intraarterial line and (2) evaluate the accuracy of systemic vascular resistance calculated from the Finapres waveform.

METHODS: Following approval of the human subjects investigation committee, 19 males and 2 females scheduled to undergo elective coronary artery bypass surgery (CABG) gave informed consent to participate in this study. These patients were free of valvular heart disease and able to sustain life without the assistance of the intra-aortic balloon pump. Patient population consisted of 2 groups: those with severe peripheral vascular disease (PVD) [n=10] and those without peripheral vascular disease (NPVD) [N=11]. The patient's thumb or middle phalanx was inserted into the Finapres cuff. The intraarterial blood pressure was measured by inserting a 20-gauge catheter percutaneously into the radial artery on the same side as the finapres cuff. Waveforms from the Finapres and the intraarterial line using the Astro-Med recorder were run simultaneously at various stages during the surgery which included preinduction, induction, postinduction, prebypass, bypass, postbypass, and completion of surgery. Anesthesia was standardized for all patients using high dose sufentanil. The area under the Finapres waveform was calculated by the trapezoidal method. This information was then applied to a modified Wesseling's formula involving the area under the pressure-time curve, which was used to calculate the SVR[1] [Fin SVR]. Simultaneously, SVR was also calculated by mean blood pressure (BP) minus central venous pressure (CVP) divided by cardiac output (CO), as measured by thermodilution, x 80 [Standard SVR]. Data was analyzed with Student's T-test, ANOVA and Pearson product moment analysis. A $P<0.05$ was considered significant. Data is presented as mean (± SD).

RESULTS: No significant differences in age, weight and sex were seen between the 2 groups. Utilizing the Finapres and arterial waveforms for both groups, no significant difference was found in systolic, diastolic and mean blood pressure. There was a significant association between the 2 methods for systolic and mean blood pressure in patients with PVD and NPVD with R^2 of 0.88 and 0.98, respectively. With respect to the 2 methods, the degree of association for diastolic blood pressure was lower in patients with PVD. The overall association between systolic, diastolic and mean blood pressures for the 2 methods yielded R^2 of 0.98, 0.86 and 0.90, respectively. The PVD group displayed a higher SVR than the NPVD group prior to induction of anesthesia as determined by the standard method (1545.8 vs. 922.0, $P<0.001$). Overall there was a significant association between the Fin SVR and the standard SVR ($R^2=0.95$, $P<0.001$) (fig. 1). In patients manifesting PVD this association was greater after the induction of anesthesia ($R^2=0.88$, $P<0.001$ vs. $R^2=0.98$, $P<0.0001$). However, in patients with NPVD, the association between the Fin SVR or the Standard SVR were both greater than $R^2=0.99$ on both occasions.

DISCUSSION: 1) The Finapres is accurate and precise in tracking the systolic, diastolic, and mean blood pressure in patients with and without PVD at various points in their operative procedure as compared to the intraarterial line. 2) The Finapres waveform when applied to Wesseling's modified equation allowed for the rapid and accurate calculation of SVR in patients with and without PVD. This finding is at odds with previous data indicating no correlation between the arterial waveform and SVR[2]. In conclusion, Finapres is a simple, non-invasive device which provides beat-to-beat hemodynamic information as accurate as those provided from an intraarterial line and a pulmonary catheter.

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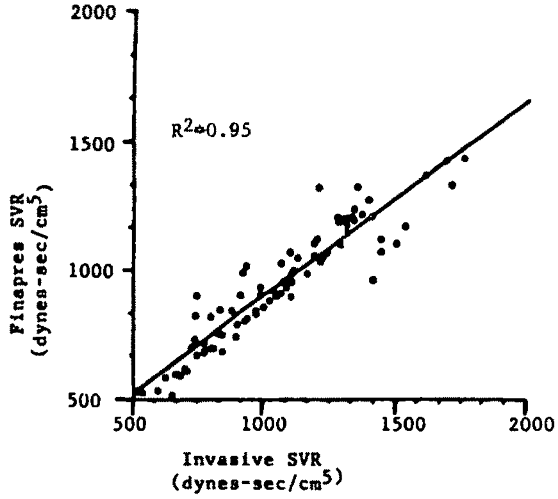
COMPARISON OF SVR DETERMINED BY FINAPRES AND STANDARD METHODS



Title: PULSE OXIMETERS CAN BE CALIBRATED NON-INVASIVELY BY END-TIDAL GAS ANALYSIS IN MAN

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Introduction: Pulse oximeters are empirically calibrated devices; their accuracy depends on in-vivo comparisons with arterial blood samples analyzed by co-oximetry. We undertook the present study to determine if estimates of arterial oxygen saturation based on end-tidal gas analysis are sufficiently accurate to be used for pulse oximeter calibration.

Methods: Ten healthy, nonsmoking volunteers, 26 to 34 years of age, with intact ulnar collateral circulation (Allen's test) consented in writing to participate in this Institutional Review Board approved study. After establishing EKG monitoring and intravenous access, we inserted a 22 ga catheter into each subject's radial artery. An Ohmeda 3700 pulse oximeter (software revision J, fast response mode) with ear probe continuously monitored oxygen saturation (Sp). Subjects breathed mixtures of oxygen in nitrogen via mask from a Mapleson D connection with fresh gas flows of 5 l/min. The associated partial rebreathing maintained end-tidal and arterial CO2 tensions in the 35-45 mmHg range, despite the increased ventilation associated with hypoxia. Gas was sampled from the mask via separate catheters for analysis of CO2 (IL 200 CO2 analyzer calibrated with 3 standard concentrations of CO2) and O2 (Godart Rapox calibrated with air and N2). The combined sampling rate was 400 ml/min, and the associated delay in analysis was approximately 5 s. A Commodore 8032 computer and 8-bit analog-to-digital converter sampled the O2 and CO2 signals 20 times per second and determined the end-tidal tensions of O2 and CO2; from these it calculated an estimate of arterial oxygen saturation (Sc) on a breath-by-breath basis using the formulae suggested by Severinghaus et al. (1). Based on the displayed values of Sc, we adjusted the delivered gas mixture to yield steady states of arterial oxygen saturation in the 65-100% range. When Sc was constant (±1%) for a full minute, we obtained an arterial blood sample while simultaneously recording Sp and Sc. We immediately placed the blood samples in an ice-water bath, and analyzed them within 30 minutes on a Corning 2500 co-oximeter, which was internally configured to display oxygen saturation as a fraction of the hemoglobin available for oxygen transport: Sa=HbO2/(HbO2+Hb) x 100. We used linear regression to determine the relationship between Sc and Sa. We also compared the bias, slope, and residual variance of the pulse oximeter calibration curve obtained by blood sampling (Sp vs. Sa) with those of the curve obtained from computed saturations (Sp vs. Sc). P<0.05 indicated significance.

Results: There were no complications or sequelae among the volunteers, although some noted reversible decreases in mental acuity when oxygen saturations were below 75%. All subjects' carboxy- and methemoglobin fractions (by co-oximetry) were less than 1.5% and 0.2% respectively. From each subject, we obtained data at 6 or 7 steady-state oxygen saturations ranging from approximately 65 to 100% (N=67). The relation between calculated (Sc) and measured arterial (Sa) oxygen saturations was Sc = 0.98 x Sa + 2.7 (r=0.98, s=2.0, P<0.001, Fig. 1). The calibration curve relating pulse oximeter reading (Sp) to calculated oxygen saturation (Sc): Sp = 1.00 x Sc - 1.0 (r=0.95, s=3.5), was essentially identical to the curve relating Sp to measured arterial saturation (Sa): Sp = 0.99 x Sa + 0.4 (r=0.96, s=3.1). Neither the slope, intercept, nor residual variance differed significantly between the two curves.

Discussion: On-line computation of oxygen saturation offers several advantages during pulse oximeter validation. First, as demonstrated by Severinghaus et al. (1), known degrees of extreme desaturation (e.g. SaO2=50%) can be obtained quickly, since the operator can adjust the inspired mixture on a breath by breath basis. Also, steady states of less extreme hypoxia can be maintained for sufficient time to allow pulse oximeter readings to stabilize--this can take 30 s or more when finger probes are used (2). Finally, we found that the computed oxygen saturations were sufficiently accurate to eliminate the need for arterial sampling during oximeter calibration. Because our subjects were nonsmokers in good health, we assumed in our computations that their acid-base status and hemoglobin dissociation curves were normal; the fact that the regression line relating Sc and Sa closely approximates the line of identity confirms the validity of these assumptions. Current pulse oximeters cannot distinguish between oxyhemoglobin (HbO2) and carboxyhemoglobin (HbCO). Their readings (Sp) are theoretically equal to the sum of the fractional concentrations of HbO2 and HbCO (3), and are within 0.5% of Sa under the conditions of our study (HbO2>65%, HbCO<1.5%). In conclusion, on-line estimation of arterial saturation from end-tidal gas is a reliable method for ensuring steady states of hypoxia, which may also allow pulse oximeters to be calibrated without the need for arterial blood samples.

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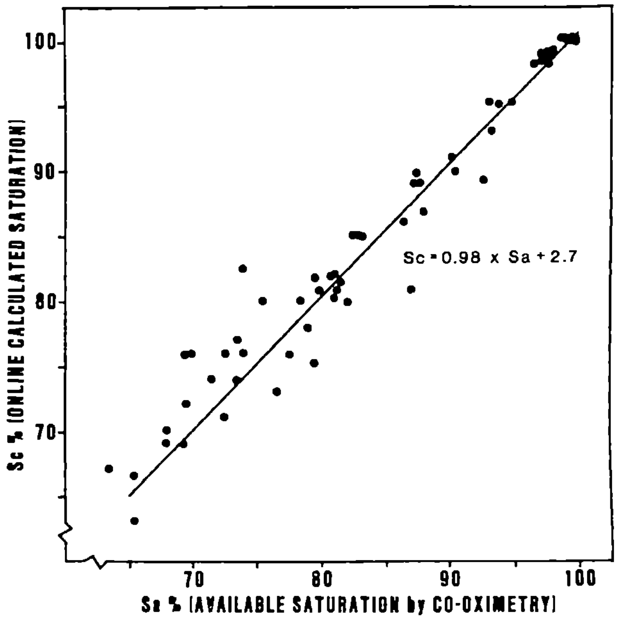

Figure 1

Title: **POTENTIATION OF THE ANTINOCICEPTIVE EFFECT OF INTRATHECAL CLONIDINE BY INTRAVENTRICULAR MORPHINE IN THE RAT**

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Introduction: Clonidine, an alpha-2 adrenergic agonist, acts as a potent analgesic when injected intrathecally or epidurally. However, at analgesic doses it can produce potentially harmful side-effects, such as hypotension, bradycardia and motor weakness.[1] One approach to minimize these side-effects is to administer another drug capable of selectively potentiating the analgesic effect. Systemic morphine has been shown to enhance the antinociceptive effect of intrathecal clonidine.[2] Because systemic morphine produces analgesia by activation of both supraspinal and spinal opiate receptors, enhancement of intrathecal clonidine analgesia may be mediated by an action of morphine at either brainstem, spinal cord or both. Potentiation of intrathecal clonidine analgesia by intrathecal morphine has already been demonstrated.[3] Whether opiate receptor activation limited to the brainstem can produce a similar potentiation is not known. This study was designed to determine if a significant antinociceptive effect can be produced by the combined administration of a subtherapeutic dose of intraventricular morphine and intrathecal clonidine.

Methods: Thirty-two male Sprague-Dawley rats (250-350 g) were anesthetized with methohexital (40-60 mg/kg ip) to permit insertion of intraventricular (IVT) cannulae and/or intrathecal (IT) catheters. Stereotactic coordinates were used to position IVT cannulae in the caudal third ventricle. IT catheters, composed of PE-10 tubing, were introduced into the subarachnoid space through a slit in the atlanto-occipital membrane and passed caudally to lie just cephalad of the *cauda equina*. Animals were allowed to recover for at least 7 days before starting experimental trials. Antinociception was measured using the tail-flick test. Heat from a projector lamp was applied to a 0.5 cm segment of the tail, with time to tail movement as the measured end-point (tail-flick latency). If no response occurred by 8 seconds, the heat was shut off to avoid tissue damage, and this value was assigned as the response latency ("cut-off"). To establish a dose-response curve for IVT morphine, 16 rats were assigned randomly to four groups. Using a blinded cross-over design, rats were tested weekly with one of four doses of morphine (0.5 µg, 1.0 µg, 2.0 µg and 4.0 µg). Measurements of tail-flick latency were made prior to injection, then every 10 minutes for 30 minutes, and again at 60 minutes. From this study and previous work,[2] subtherapeutic doses of IVT morphine (0.5µg) and IT clonidine (5µg) were chosen. In the second experiment, 16 rats were divided randomly into four groups. Employing a blinded cross-over design, each group received weekly concurrent IVT and IT injections of one of the four following combinations: 1) IVT and IT saline; 2) IVT morphine/IT saline; 3) IVT saline/IT clonidine; 4) IVT morphine/IT clonidine. IVT and IT injections were performed over 30 seconds using a volume of 2µl and 5µl, respectively. IT injections were followed by 10 µl of saline to flush the catheter. Measurements of tail-flick latency were made prior to injection, then every 10 minutes for one hour, and again at 90 minutes. At the end of the study, correct placement of cannulae and catheters was confirmed by IVT injection of 2µl methylene blue and IT injection of 5µl carmine red. Thirty minutes later, animals were sacrificed and brains sectioned to determine extent of staining. For data analysis, response latencies were converted to "percent maximum possible effect", where %MPE = [(post-injection latency - baseline latency) ÷ ("cut-off" - baseline latency)] x 100. Differences among the four treatment groups were determined using ANOVA and Scheffe's test for multiple comparisons, with $p<0.05$ considered significant.

Results: Results are depicted in figures 1. Tail-flick latencies did not significantly deviate from baseline in rats that received injection of IVT morphine/IT saline, IVT saline/IT clonidine, or IVT saline/IT saline. However, the antinociceptive effect of the IVT morphine/IT clonidine combination was significantly different when compared to baseline ($p<0.001$), or to the other control groups ($p<0.01$). This effect was apparent at 10min, peaked at 50min, and persisted for 90min. None of the animals that received both IVT and IT saline attained cut-off. This limit was reached by only 8% of the IVT saline/IT clonidine group and 15% of the animals receiving IVT morphine/IT saline. In contrast, combined administration of IVT morphine and IT clonidine resulted in 85% of the animals reaching the maximum flick-latency. Dye-injection studies failed to demonstrate IVT staining below the 4th ventricle, or IT staining higher than the thoracic cord. Dye was not observed in the 3rd ventricle of two rats, and data from these animals were excluded from the study.

Discussion: Morphine's activation of brainstem opiate receptors produces inhibition of pain transmission at the spinal cord via descending neural pathways. The present study demonstrates that morphine acting at these supraspinal sites, without a direct action at the spinal cord, has a greater than additive effect on intrathecal clonidine antinociception. It suggests that activation of either brainstem or spinal cord sites is sufficient to account for the potentiation of IT clonidine analgesia observed with systemic morphine.

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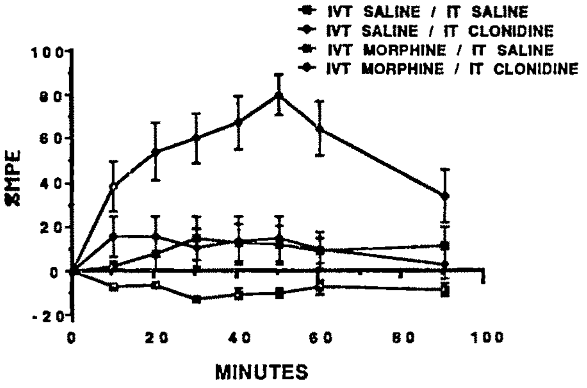

Figure 1. Data are expressed as mean +/- SEM.

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Title: LOWER ESOPHAGEAL CONTRACTILITY AS A GUIDE TO ANESTHETIC DEPTH MANAGEMENT

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Introduction. Accurate assessment of depth of anesthesia has been an elusive goal throughout the history of anesthesia. Extreme anesthetic overdose is detectable by cardiovascular depression, but relative overdose can prolong awakening and recovery room stay. Underdosing can also pose serious threats due to hemodynamic stress and/or awareness and recall. Devices designed to measure and deliver precise concentrations of anesthetic gases have been developed and have evolved significantly. However, inter-patient variability in uptake, distribution and sensitivity to anesthetic drugs make it difficult to predict depth of anesthesia solely on the basis of dosing, or inspired or expired anesthetic gas concentrations. Clinical signs of anesthetic depth first developed for diethyl ether (pupil size, lacrimation, sweating, movement, grimacing) as well as cardiovascular changes may be blunted or unavailable due to modern multi-drug approaches which include neuromuscular and autonomic blockers, amnestics and narcotics. Other factors have increased the need for better depth assessment. Longer, more complex surgical procedures are performed on younger, older, and sicker patients. In addition, outpatient surgery for routine procedures is becoming more prevalent. Fine tuning depth of anesthesia is desirable to reduce traumatic deviations from homeostasis during long procedures, enable faster recovery from anesthesia for same-day release, and reduce costs by using less anesthetic and hospital time. EEG has been used to monitor anesthetic depth, however EEG suffers from problems which include huge inter-patient and drug response variability, hassle of multiple electrode placement, and ambiguous interpretation, even with spectral arrays. Measurements of lower esophageal contractility (LEC) were reported in 1984 to correlate with general anesthetic depth (1). In humans, the lower third of the esophagus is composed of smooth muscle which is immune to the effects of neuromuscular blocking drugs. LEC is an index of brainstem activity and anesthetic depth, and an esophageal contractility monitoring system (American Antec) has been developed. The LEC probe also includes an esophageal stethoscope for monitoring of patients breath and heart sounds. In this study we evaluated the utility of LEC as a guide to the management of anesthetic depth in 2 phases. Phase I consisted of surgical patients who received LEC monitoring in addition to routinely monitored parameters to establish a normal range of ECI. Phase II consisted of patients whose anesthetic dosing was guided by ECI criteria. ECI criteria for dosing resulted in adequate anesthesia and lower total anesthetic delivery with no incidents of awareness or recall.

Methods. The esophageal probe has a fluid- filled balloon at its tip which senses contractions and transmits them to the monitor via a fluid-filled catheter. In addition, an inflatable balloon located several centimeters above the tip is air-inflated abruptly at regular intervals to provoke contractions. The device displays the esophageal contractility index (ECI) which reflects the frequency of spontaneous lower esophageal contractions (SLEC) and the amplitude of provoked lower esophageal contractions (PLEC) as follows:

$$\mathrm{ECI} = 70 * \mathrm{SLEC}\ \frac{(\text{contractions})}{(\text{minutes})} + \mathrm{PLEC}\ (\text{torr})$$

Thus ECI is a numerical index of both spontaneous and provoked LEC and an (inverse) indicator of anesthetic depth.

With Human Subjects Committee approval and informed consent, 22 patients have been studied thus far. Phase I consisted of 13 surgical patients who received LEC monitoring in addition to the routinely monitored physiological parameters. Patients were premedicated with IV midazolam, induced with standard doses of sodium thiopental and vecuronium, and maintained with isoflurane and nitrous oxide. 100 micrograms of fentanyl were also administered. ECI was recorded every 3 minutes along with heart rate (HR), blood pressure (BP), end-tidal anesthetic (ETA), and EEG spectral edge frequency (SEF). In addition, several measures of recovery from anesthesia were utilized including Aldrete scores, Lafayette test, and an evaluation questionnaire. LEC was recorded but not used in the clinical management of patients in Phase I. ECI values between 30 and 120 were found to correlate with "surgical" anesthesia. Phase II consisted of 9 patients receiving the same premedication, induction and anesthetic as in Phase I except nitrous oxide was omitted. These patients, however, had their isoflurane vaporizer titrated to their LEC ECI. Once stable anesthesia was achieved and the surgical procedure had begun, the anesthesiologist was asked to adjust isoflurane concentration to keep the ECI in the range 30-120 (unless this violated his/her clinical judgement). If the ECI remained above 120 for 9 minutes (3 observations), isoflurane concentration was increased by .25%. Conversely if ECI fell below 30 for 9 minutes, isoflurane concentration was decreased by .25% This protocol was to be followed subject to additional intervention for heart rate less than 60 or greater than 100, or systolic BP less than 70 or greater than 160.

Results and Conclusions. Using ECI criteria for dosing resulted in adequate anesthesia for the 13 patients in group II. Hemodynamic parameters exceeded the criteria for intervention 11 times in 14.75 hrs. of surgery for group II. ECI dosing criteria were also superceded 3 times at the discretion of the anesthesiologist who felt that patients might be too "light". No statistically significant differences were found between the two groups regarding ECI, ETA, HR, BP, SEF, or any of the recovery measures employed. Phase I patients received average MAC equivalents (per time) of 1.38 ± 0.21 (mean ± S.D.) whereas Phase II patients received average MAC equivalents of 0.90 ± 0.24 (mean ± S.D.). By Student's t test, these values differed at a significance level of $p < 0.05$. Thus, Phase II patients who had their isoflurane titrated by LEC ECI consumed significantly less total anesthetic. We conclude that LEC ECI can be a valid index of anesthetic depth and its use can reduce anesthetic consumption without risk of awareness or recall.

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Title: EFFECT OF CENTRAL VENOUS PRESSURE ON BRAIN COMPLIANCE

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Introduction. Post-traumatic intracranial hypertension is a significant cause of morbidity and mortality. Cerebrospinal fluid dynamic studies by Marmarou and colleagues have shown that elevation of intracranial pressure (ICP) is generally preceded by a decrease in total brain compliance as measured by the relative rise in pressure for a given increase in volume $(\partial P/\partial V)$ (1). The relationship between the compliance of the intracranial compartment and total intravascular volume has yet to be adequately defined. Alterations in brain compliance as a function of central venous pressure were studied in miniature swine.

Methods. Sexually mature, female Yucatan Minipigs weighing 14.0 to 15.5 kilograms were pre-medicated with xylazine (2mg/kg) and atropine (0.08mg) IM. Induction of anesthesia with ketamine (15mg/kg) IM was followed by an air/oxygen mixture adjusted to maintain PaO2 at 100-120 torr with 1.5-2.0% Forane via endotracheal tube. Expired CO2, O2, and Forane concentrations, peak inspiratory pressures and temperature were monitored continuously, as were arterial blood pressure, central venous pressure (CVP), and urine output after placement of femoral arterial and venous lines, internal jugular central venous catheter, and bladder drainage via cystostomy. In some cases a flow-directed pulmonary artery catheter was placed also. A right anterior ventriculostomy was made with an 18 gauge Teflon catheter passed at right angle to the skull at the coronal suture, cemented in place with methyl-methacrylate, and connected to a three-way stopcock for fluid infusion and pressure monitoring. A Camino fiberoptic pressure transducer was placed in the contralateral anterior ventricle for continuous ICP monitoring. A midline 5 millimeter craniotomy was made either 3 cm. anterior to the bregma or 2 cm. anterior to the lambda for cannulation of the sagittal sinus for continuous pressure monitoring and sampling. Animals in Group I (n=5) were maintained NPO for 12 hours prior to expermentation while Group II (n=5) were allowed continued access to water. Brain compliance was calculated from the rise in intracranial pressure following a 1 cc intraventricular bolus of normal saline. Central venous pressure was elevated above baseline values by infusion of 5% dextrose in 0.45% normal saline solution.

TABLE 1

	GROUP I	GROUP II
Mean ABP	90.5 +/- 1.7	91.0 +/-2.1
pH	7.48 +/- .020	7.50 +/- .020
pCO2	37.9 +/- .52	37.3 +/- .80
CVP	6.3 +/- .37	9.3 +/- .14
ICP	7.6 +/- 1.3	8.9 +/- 1.9
SSP	6.3 +/- .45	9.8 +/- .80

Results. Baseline physiologic parameters are demonstrated in Table 1. There was no significant difference in mean arterial blood pressure, arterial blood gas values, CVP, sagittal sinus pressure or ICP between animals from Groups I or II. PCWP was 6.5 +/- 1.5mm Hg irrespective of CVP or compliance changes. Similarly, there was no correlation between sagittal sinus and central venous pressures. However, analysis of brain compliance demonstrated a significant ($p < .025$) decrease as a function of increasing central venous pressure as can be seen in Figure 1. This relationship can be described as a logarithmic curve fitting the equation :

$$y = 0.377 * \text{x\textasciicircum-1.115} \quad R = 0.79$$

Attempts at increasing the central venous pressure above 12.5 mm Hg resulted in increased mean arterial blood pressure hence elevation of CVP above this level was not employed in these studies.

Discussion. Traumatic Brain Injury is often associated with multiple injuries as well as hypovolemia secondary to hemorrhage. Vigorous resuscitation with volume expanders such as crystalloid may improve mean arterial blood pressure yet volumes necessary to do so may significantly increase central venous pressure. Brain compliance is the summation of the ability of several intracranial compartments to "buffer" increases in intracranial volume. This increase in CVP may increase cerebrovascular venous outflow resistance resulting in a decrease in the ability of this compartment to tolerate an increase in intracranial volume with a result similar to compartment syndromes described elsewhere. Our findings suggest that intravascular volume expansion above PCWP significantly decreases brain compliance. Therefore, hypervolemic states may contribute to intracranial hypertension following traumatic brain injury and resuscitation.

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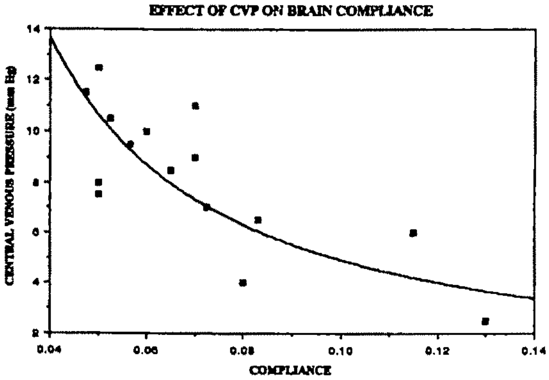
Figure 1



Title: INTRATHECAL MORPHINE FOR POSTOPERATIVE ANALGESIA IN CHILDREN

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Introduction. Intrathecal morphine provides reliable postoperative analgesia at the expense of frequent unwanted side effects (1,2). Few studies have examined the effects of intrathecal morphine in children. One report suggested it provided prolonged postoperative analgesia with relatively infrequent side effects (3). We report preliminary results in children undergoing spinal surgery.

Methods. Consent was given by the parents for 15 consecutive children, ages 2-9, scheduled for dorsal rhizotomy to receive intrathecal morphine for control of postoperative pain. Induction of general anesthesia was accomplished by mask inhalation of halothane or by rectal administration of brevital. Endotracheal intubation was facilitated by succinylcholine; and anesthesia was maintained with halothane, nitrous oxide, and oxygen. No intravenous narcotics or sedatives were administered. At the conclusion of the operative procedure, the dura was closed, the subarachnoid space filled with a saline solution, and the calculated dose of preservative free morphine injected at the S_2 level. The initial dose of intrathecal morphine, 7 ug/kg, was derived from reports in adults. Subsequent patients received increasing doses until a dose response curve could be determined. Postoperative assessment was conducted by nurses who were unaware of the dose administered to each child. Pain was assessed by means of a visual analogue scale, by observation, and by direct questioning. All children were assessed for clinical signs of respiratory depression, pruritis, and nausea/vomiting.

Results. The 15 children received doses of intrathecal morphine ranging between 7 and 23 ug/kg. The duration of postoperative analgesia was extremely variable. No dose response could be characterized, and duration of analgesia ranged between 6 and >48 hours (Table 1). Immediate respiratory depression requiring naloxone occurred in one patient shortly after injection. No child displayed late respiratory depression. Three children (20%) experienced nausea/vomiting, and none had pruritis.

Discussion. Selective rhizotomy is a relatively new procedure indicated for treatment of spasticity due to cerebral palsy. It requires prolonged postoperative analgesia. Intrathecal morphine is an attractive alternative to parenteral narcotics. Jones et al reported that intrathecal morphine produced prolonged postoperative analgesia in children recovering from cardiac surgery (3). In their study, both 20 and 30 ug/kg resulted in greater than 12 hours of analgesia in 90% of patients while 40% were pain free for greater than 24 hours. In contrast, only 40% of neurosurgical patients obtained greater than 12 hours of postoperative analgesia and only two patients (13%) were pain free at 24 hours. One explanation for the apparent discrepancy between the duration of action in the two studies is the supplemental medication given cardiac surgical patients. Heavy preoperative sedation and frequent intraoperative narcotics were part of the anesthetic plan and may have either prolonged the effect of intrathecal morphine or complicated the postoperative assessment. An alternative hypothesis is that morphine leaked from the long dural incision (from L_2 to S_2), and the concentration of drug reaching the rostral central nervous system was reduced and the duration lessened.

Intrathecal morphine, 10-20 ug/kg, produces prolonged analgesia in adults but is often accompanied by pruritis, nausea/vomiting, respiratory depression, and urinary retention (1). In contrast, only 20% of children recovering from posterior rhizotomy experienced nausea or vomiting, and no child had itching. This is similar to data presented by Jones et al (3). They observed a 20% incidence of nausea/vomiting, a 16% incidence of respiratory depression, and occasional itching. Both the study by Jones et al and these preliminary data suggest that unwanted side effects following intrathecal morphine occur less frequently in children. Whether these differences among adult and pediatric patients reflect the relative greater CSF volume of distribution in the child or different end organ sensitivities remains to be determined. The optimal dose of intrathecal morphine in children awaits clarification.

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Table 1

Patient	Dose (ug/kg)	Weight (kg)	Age (years)	Duration of Action (hours)	Side Effects
1	7	22	8	12	None
2	8	18	5	9	None
3	9	19	9	6	None
4	9	12	3	8	Nausea
5	11	20	6	13	Nausea
6	12	13	2	-	Arrest
7	15	17	7	6	None
8	17	14	4	8.5	None
9	17	11	3	25.5	None
10	19	14	5	>48	None
11	19	12	2	6	None
12	19	14	2	18	None
13	21	13	2	7	None
14	21	11	3	18	Nausea
15	23	11	3	7	None

Title: ICP- AND IOP EFFECTS OF DELIBERATE HYPOTENSION USING URAPIDIL -- AN EXPERIMENTAL STUDY IN SWINE

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Introduction. Deliberate hypotension is an accepted method to facilitate certain neurosurgical and intraocular procedures. The rationale is to reduce transmural pressure on arterial vessels and thus to facilitate preparation of cerebrovascular aneurysms and malformations - or in ophthalmology to reduce the risk of expulsive bleeding (1).
Classical hypotensive agents are known to increase intracranial pressure (ICP) which adversely affects cerebral perfusion pressure (CPP) until the dura is open (2).
We have investigated effects of the new sympatholytic urapidil* on hemodynamics, ICP, IOP and pulmonary function.

Methods. The protocol was approved by the institutional animal investigation committee. Ten German landrace piglets (bw $\bar{x}$ 26kg (23-29)) were premedicated (azaperone 8mg/kg i.m.), anesthetized (piritramide; induction: 1mg/kg i.v.; maintenance: 2mg/kg/h p.inf.), intubated and instrumented (arterial line, Swan-Ganz catheter, ventricle catheter, anterior chamber cannula). Ventilation was controlled by end tidal capnometry (volume controlled ventilator, 60% N_2O in O_2). Control measurements were performed and repeated when a reduction of mean arterial pressure (MAP) by 50 % was achieved or when the maximum dosage of 4mg/kg was administered. Derived parameters were calculated using standard formulae. Statistical evaluation utilized the t-test.

Results. MAP could be reduced to $\geq$ 50 mmHg, irrespective of baseline; indicating that a reduction by 50% was not achieved in all pigs. ICP and IOP did not increase, cardiac output (CO) increased (+ 15%), systemic vascular resistance (SVR - 10%) and central venous pressure (CVP) decreased. In contrast pulmonary artery pressure (PAP + 21%) and pulmonary vascular resistance (PVR + 24%) increased. All measures returned to baseline $\leq$ 10 min. following discontinuation of urapidil infusion. Neither unwanted hypotension nor compensatory hypertension were observed.

*Ebrantil^{TM} (Byk Gulden, Konstanz, FRG)

Discussion. Urapidil reduces MAP (but not PAP) when administered at a dosage of 2 - 4 mg/kg to anesthetized pigs (Fig. 1). Myocardial performance is improved, pulmonary function is not affected. Arterial hypotension is short lived, easily controlled and not associated with a rise in ICP or IOP. Urapidil appears to be a suitable agent when moderate and short lasting arterial hypotension is indicated and when an increase in ICP/IOP (or uncontrolled hypotension) are to be avoided. This could apply to patients with brain injury and intracerebral hemorrhage (3) that are at risk of hypertension.

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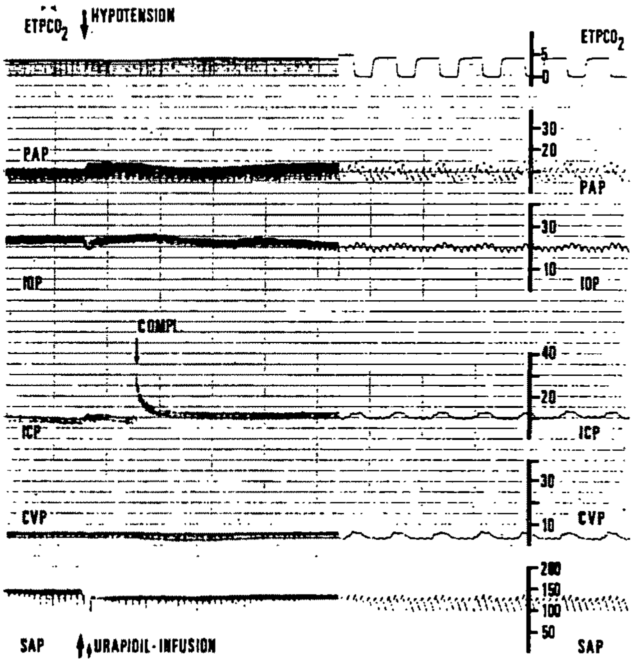

TITLE: COMPARISON OF THE CELL SAVER WITH THE HEMOFILTER FOR BLOOD SCAVENGING AND CONSERVATION IN CARDIAC SURGERY

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Introduction. Blood scavenging techniques have decreased the need for perioperative homologous blood transfusion in cardiac surgery patients. The efficacy and importance of minimizing transfusion therapy is a timely issue. Previous studies have investigated the use of the Cell Saver (CS)[1,2]. Single pass ultrafiltration (SPUF) has been used to concentrate blood in the cardiopulmonary bypass (CPB) machine[3,4]. This study compares the use of SPUF with the CS as a complete method of blood scavenging and conservation.

Methods. The protocol was approved by the Committee for the Protection of Human Subjects. Written informed consent was obtained. The subjects were coronary artery bypass (CABG) patients over 35 years of age randomized to a CS or SPUF group. Excluded were patients scheduled for "re-do" or emergency operations, other cardiac operations, those with coagulopathies, insulin dependent diabetes, creatinine > 1.6, and patients with intra-aortic balloon pumps in place. Patients were anesthetized with oxygen, fentanyl and relaxant following placement of intravenous, arterial and pulmonary artery catheters. Blood was scavenged via a heparinized suction system into a cardiotomy reservoir. All scavenged blood and the remaining oxygenator blood were processed following weaning from CPB and used as needed. The blood was processed according to the manufacturers' instructions in a Cell Saver IV with 1000ml normal saline wash. SPUF was done using Cobe Model 1200 Hemofilter, average molecular weight cutoff 55,000D, perfused by a roller head on the CPB machine (rate of 150ml/minute, negative transmembrane pressure 450mmHg). Patients were given only processed blood. Homologous blood was used only if the hematocrit (Hct)< 16 on CPB, Hct< 24 in the perioperative period, or for active bleeding. A CBC, partial thromboplastin time (PTT), prothrombin time (PT), thrombin time (TT) and free hemoglobin (fHgb) were measured pre-operatively, post CPB (following protamine reversal and return of the ACT to baseline), 30 minutes after infusion of all processed blood, on postoperative day (POD) one and five. These tests were also done on specimens of SPUF or CS processed blood. Heparin assays were only performed immediately post-CPB, 30" post reinfusion and on processed blood. Post operative chest tube drainage, transfusions required (scavenged and homologous), weight on POD 1 and postoperative complications were recorded. Comparisons were made between the groups with chi square test of significance for dichotomous variables and with a t-test for continuous variables.

Results. 52 patients were enrolled; 27 were in the CS and 25 were in the SPUF group. There was one death in each group; these patients were excluded from the analysis. There were no baseline differences in age, sex, weight, preoperative medications, CPB time, or laboratory parameters between the two groups. There was no statistical difference at any time in the hemoglobin (Hgb), Hct, or platelet (PLT) count between the two groups. No statistical difference was found between groups in weight on POD 1, total transfusions required in hospital, or in the complication rate. The PTT and TT were elevated significantly in the SPUF group 30" post infusion of processed blood ($p<.05$). Heparin levels with SPUF were higher, in both the processed blood and 30" post infusion ($p<.05$). SPUF patients received significantly more protamine in the operating room. SPUF patients had significantly greater blood loss from the chest tubes than CS patients at 24 hours (1632ml vs 1054ml, $p<.01$). However the total blood loss prior to removal of the chest tubes was not different. fHgb was elevated in the SPUF group 30" after reinfusion ($p<.01$) but there was no difference in fHgb on POD 1 or 5.

Discussion. The elevated PTT and TT in the SPUF group 30" following reinfusion of processed blood is consistent with the increased heparin levels found in the SPUF patients. Despite the elevated PTT, TT, and higher blood loss at 24 hours in the SPUF group, total blood loss, Hct, and PLT count were similar in the two groups, suggesting that the early blood loss in SPUF patients was not clinically significant. There was no statistical difference in total transfusion requirements between the two groups. The coagulation abnormalities noted in the SPUF group can best be explained by the processing method. The CS washes out most of the heparin used for anticoagulation during scavenging whereas SPUF, being a filtering and concentrating system, does not. It is possible that the use of citrate as an anticoagulant for the blood scavenging system could have eliminated even these differences. The increased fHgb in the SPUF group reflects a concentrating versus a washing method. Blood trauma with SPUF may also be a cause of the phenomenon. However, there were no differences in fHgb at subsequent times and no evidence of renal failure in either group.

We conclude that the CS and the SPUF systems are both safe and reliable for complete blood scavenging in the cardiac surgery population described. The differences observed may be eliminated by using a different anticoagulation system.

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Title: ALTERATIONS IN SPINAL CORD AND CEREBRAL AUTOREGULATION DURING HALOTHANE ANESTHESIA IN THE RAT.

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Introduction. Volatile anesthetic agents have been shown to alter the cerebral vasculature's ability to autoregulate, a mechanism which maintains tissue blood flow relatively constant despite variations in perfusion pressure. Halothane, as a potent vasodilator, has been shown to modify cerebral autoregulation in a dose dependent fashion, such that low dose halothane may alter the normal autoregulatory curve while high dose halothane abolishes it completely. The effect of halothane on autoregulation of spinal cord blood flow, however, has not been well elucidated. The purpose of this study was to measure spinal cord blood flow (SCBF) under conditions of varying mean arterial blood pressure to determine the effects of halothane on spinal cord autoregulation. Cerebral blood flow (CBF) will be measured simultaneously to allow a comparison between the effects of halothane on the brain and the spinal cord.

Methods. Twelve adult rats weighing 444-503g were anesthetized by the inhalation of halothane. They were intubated and ventilated with air and oxygen to maintain arterial blood gases within normal physiological limits. Anesthesia was maintained with 1% halothane and the animals were paralyzed with 0.2mg/kg of pancuronium. Catheters were inserted into the right femoral artery for arterial blood gas samples and continuous monitoring of arterial pressure and into the left femoral vein for intravenous drug administration. A left ventricular catheter was placed retrograde from the right carotid artery to be used for microsphere injections to determine blood flow. Central venous pressure was measured by a catheter placed in the left jugular vein. Mean arterial pressure (MAP) was either raised or lowered by a neosynephrine (160 ug/ml) or trimethaphan (4 mg/ml) continuous intravenous infusion. Blood flows were then measured at varying levels of MAP. Approximately 0.3ml of microsphere solution (^{125}I, ^{141}Ce, ^{85}Sr, ^{46}Sc) was injected into the left ventricle. Reference arterial blood samples were withdrawn from the femoral artery beginning immediately prior to injection and continuing for one minute after initiation of the injection. The brain and spinal cord were removed after completion of the microsphere injections and gamma analysis of the tissue sections was performed. Blood flows were then obtained by computer calculation. Polynomial regression analysis was used to determine the best fit through the data points obtained with calculation of a correlation coefficient (r) and p value for evaluation of statistical significance of the relationship between blood flow and perfusion pressure. Significance was taken to be $p<.05$. This study was approved by the Animal Care Committee, University of Texas Health Science Center in San Antonio.

Results. Arterial blood gases remained within normal physiological limits. Mean PaO_2 was 116.6$\pm$4.3(SEM), mean $PaCO_2$ was 37.9$\pm$0.4, and mean ph was 7.37$\pm$.01. The graphic relationship between perfusion pressure (PP) and blood flow demonstrated that anesthesia with 1% halothane modified brain and spinal cord autoregulation, but did not abolish it completely (Figure 1). CBF and SCBF remained relatively constant between 50 and 100 mmHg PP at 98.5$\pm$8.3ml/100g/min and 95.3$\pm$10.2ml/100g/min respectively. There was no significant difference between CBF and SCBF within this autoregulatory range. Below 50 mmHg and at 100mmHg or above, changes in CBF and SCBF paralleled changes in PP. The lowest flows measured were 25ml/100g/min for the brain and 22ml/100g/min for the cord at a PP of 30mmHg. The highest flows measured were 361ml/100g/min for the brain and 353ml/100g/min for the cord at a PP of 130mmHg. The autoregulatory curves established for the brain and cord appeared virtually identical (Figure 1).

Discussion. Autoregulation was altered by halothane in both the brain and the spinal cord. The perfusion pressure range over which autoregulation occurred was narrower and shifted to the left compared with previous studies in barbiturate anesthetized rats.[1] The vasodilating properties of halothane most likely explain this modification of cerebral autoregulation. Spinal cord autoregulation was affected by halothane in a manner similar to the brain. Although the slight reduction in the lower limit of autoregulation could lead to enhanced cerebral or spinal cord blood flow at a lower perfusion pressure, the effect of the reduction in the upper threshold for autoregulation could have deleterious consequences. In the brain, this could potentiate an elevation in intracranial pressure during episodes of arterial hypertension. Similar adverse consequences might also be seen in the spinal cord, particularly in instances in which intraspinal compliance is reduced.

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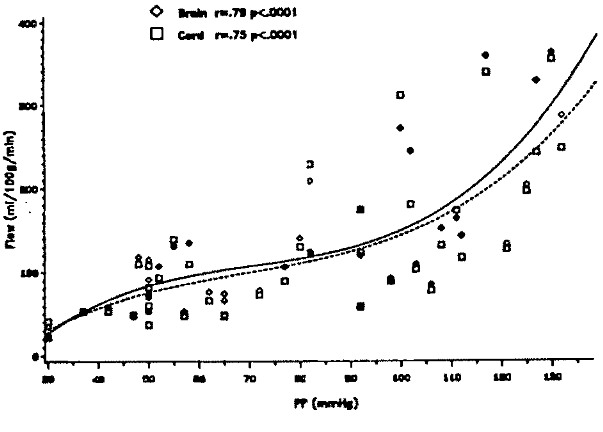

Title: KETAMINE ABOLISHES CENTRAL NERVOUS SYSTEM AUTOREGULATION IN THE RAT

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Introduction: Among the intravenous anesthetic agents, ketamine is unique in its effect on cerebral vascular dynamics. As a potent cerebral vasodilator, it has been shown to cause an abrupt elevation in cerebral blood flow (CBF) that has been associated with marked elevations in intracranial pressure.[1] The effect of ketamine on cerebral autoregulation, however, has not been previously examined. The purpose of this study was to measure cerebral blood flow under conditions of varying mean arterial pressure to determine the cerebral vasculature's capacity to autoregulate during ketamine anesthesia. Spinal cord blood flow (SCBF) was also measured to determine if ketamine effects the ability of the brain and spinal cord to autoregulate in a similar fashion.

Methods: Twelve adult rats (280-530g) were anesthetized with intraperitoneal ketamine 160mg/kg. The animals were intubated and ventilated with air and oxygen to maintain normoxia and normocarbia. Arterial blood pressure was monitored by a catheter inserted in the right femoral artery and central venous pressure was measured by a catheter inserted into the right jugular vein. A left femoral vein catheter was inserted for intravenous drug administration. A left ventricular catheter was placed under direct vision following a sternotomy. This catheter was to be used for microsphere injections (^{125}I, ^{141}Ce, ^{85}Sr, ^{46}Sc) in order to measure blood flow. The animals were paralyzed with pancuronium bromide 0.2mg/kg and maintained on a continuous intravenous infusion of ketamine 2mg/kg/hr. Blood flow measurements were then made in each animal at varying levels of mean arterial pressure (MAP), which was altered by an intravenous infusion of trimethaphan to lower MAP or neosynephrine to raise MAP. The brain and spinal cord were removed and sectioned for gamma analysis. Blood flow was calculated as:

F = (CT/CB) X 100
F = tissue blood flow (ml/100g/min)
CT = counts/gram of tissue
CB = counts/ml/min of reference arterial blood.

Average brain and spinal cord blood flows were determined by pooling data from the individual brain and cord sections. Perfusion pressure (PP) was then plotted against blood flow and using linear regression analysis, best fit lines through the data points for both the brain and the spinal cord were obtained. A correlation coefficient (r) and p value ($p<.05$ considered significant) were calculated to determine the significance of the relationship between blood flow and PP. This study was approved by the Animal Care Committee, University of Texas Health Science Center in San Antonio.

Results: Arterial blood gases remained within normal physiological limits. Mean $PaCO_2$ was 38.0±0.7(SEM) and mean ph was 7.38±.01. Mean PaO_2 was 140.6±10.1. Changes in perfusion pressure (PP) paralleled changes in blood flow for both the brain and spinal cord. A minimum flow of 8ml/100g/min for the brain and 8ml/100g/min for the cord was noted at the lowest PP measured (4mmHg). Flow increased linearly with further increases in PP to a maximum CBF of 802ml/100g/min and SCBF of 787ml/100g/min at the highest PP measured (189mmHg). A graphic comparison of the relationship between PP and blood flow for the brain and spinal cord were made. These linear relationships appear to be virtually identical (Figure 1).

Discussion: Our data demonstrate that the cerebral vasculature's ability to autoregulate is abolished by ketamine. Increases in perfusion pressure were accompanied by marked elevations in blood flow, with a linear relationship between flow and pressure present in the brain. Previous studies have demonstrated that the spinal cord mimics the brain in its autoregulatory capacity under thiopental anesthesia.[2] Our present data also indicates that the brain and spinal cord behave similarly, although both lacking autoregulatory capability under ketamine anesthesia. The animals that were used in this study were without intracranial or intraspinal pathology. The need remains to establish the effects of ketamine on autoregulation of blood flow in pathological cerebral or spinal cord states. It is probable that the adverse effects of ketamine on autoregulation would be even more pronounced in instances of comprised intracranial or intraspinal compliance.

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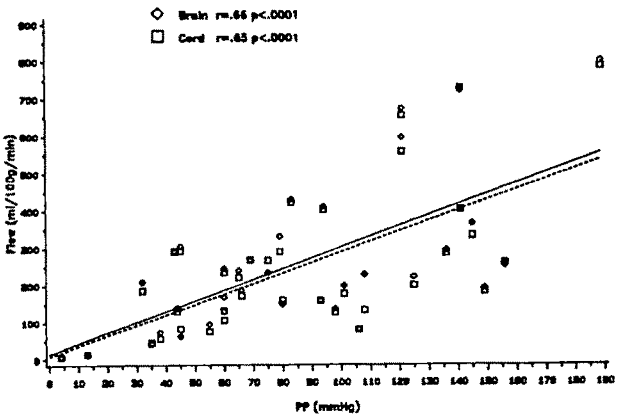

Title: LOWER INCIDENCE OF INTRAVENOUS CATHETER COMPLICATIONS WITH AN ELASTOMERIC HYDROGEL CATHETER

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Introduction. Approximately 70% of all hospitalized patients in the U.S. receive i.v. therapy compared to 25% reported only ten years ago. Despite the many benefits of this therapy, complications ranging from phlebitis to fatal sepsis continue to occur. The development of these complications has been related to a number of factors, including the methods of insertion and site maintenance, the duration of catheterization, the age and general condition of the patient, and the material used in construction of the i.v. cannula. Recently, a new hydrogel material, Aquavene®, has been developed which undergoes predictable softening and dimension changes within 30 minutes of contact with aqueous fluids. An intravenous catheter made of this material (Streamline® catheter, Menlo Care, Palo Alto, CA) is rigid when dry, but becomes soft and pliable when exposed to bodily fluids. Thus the rigidity required for insertion is available, but the catheter softens after insertion, which could minimize irritation or perforation of the venous intima. Additionally, these catheters predictably expand by two gauge sizes after insertion, which may be advantageous. To prospectively test whether the hydrogel catheter causes fewer intravenous catheter complications, we measured the incidence of complications in 104 hospitalized patients randomly assigned to receive either catheter.

Methods. After approval by our human experimentation committee, a prospective study of 104 patients requiring intravenous catheters was conducted. Surgical patients who were expected to require greater than 24 hours of i.v. therapy were randomly assigned to receive a Menlo Care catheter (20 gauge, expands to 18 gauge), or a standard teflon catheter (control, Jelco^{TM} 18). We measured the incidence of phlebitis, infiltration and other complications in the two groups, as well as the dwell time before any complications developed. Essentially all complications consisted of phlebitis or infiltration, although there were rare or isolated instances of kinks/twisting, leakage, clotting and "slipout." We evaluated phlebitis using a standardized scale (1), and infiltration by local swelling and failure to obtain blood on aspiration. Catheters were evaluated daily by the nurse caring for the patient and findings were confirmed by a member of our research group. The decision to remove a catheter when the catheter site showed phlebitis or infiltration was made by the clinical team caring for the patient. Results were analyzed by Fisher's Exact Test, or the Mann-Whitney U test, where appropriate. *p* values less than .05 were considered significant.

Results. Summarized in Table 1.

Table 1: Intravenous Catheter Complications

	Menlo (n=49)	Control (n=55)	*p* =
# of Catheters Removed for Site Complications:	13	28	.01
Median Time to Development of any Complication (hours):	101	79	<.05
# of Infiltrated Catheter Sites:	1	10	0.014
# of Catheter Sites Developing Phlebitis:			
Total:	16	22	.50
First 72 hours:	3	9	.10

Catheter removal for any complication was required significantly less frequently in the test group (28% of Menlo Care catheters) than in the control group (51%). The median catheter dwell time before development of i.v. site complications was 22 hours longer in the test group than in the controls. Infiltration of the i.v. site was much less common in the test catheter group (2%) than in the control group (18%). When all episodes of catheter-site phlebitis are considered, 32% of the test group and 40% of the control group developed this complication (p = not significant). During the first 72 hours of i.v. therapy, there was a trend toward less phlebitis in the test group (6% vs. 16% in the control group), but this trend did not reach statistical significance ($p = .10$).

Discussion. Intravenous catheters constructed of an elastomeric hydrogel material have the advantage of expanding two gauge sizes after insertion. These catheters caused i.v. site infiltration significantly less frequently than a standard teflon catheter in this group of surgical patients. Although the overall incidence of catheter site phlebitis was not different between the hydrogel and teflon type catheters, phlebitis may take longer to develop at hydrogel catheter sites.

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Title: AMBULATORY SURGICAL COMPLICATION IN THE POSTOPERATIVE PERIOD: WE CAN'T JUST WALK AWAY

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Introduction. Recent evidence has demonstrated that the incidence of complications occurring during the post anesthesia recovery room (PAR) stay is higher than previously expected.[1] Historically efforts to determine factors associated with PAR complications of the ambulatory surgery patient have been aimed primarily at defining the incidence of nausea and vomiting.[2] To date, no study has been designed to investigate the overall incidence of intraoperative and recovery room complications occurring in the ambulatory surgery PAR. Therefore, as part of our on going quality assurance program, we designed a study to evaluate the incidence of complication occurring in ambulatory surgical PAR.

Methods. Following approval of the Human Investigation Committee, a prospective study of 3,477 (n = 3,477) consecutive patients entering the ambulatory surgery PAR was performed. Data was collected using a standard form developed to determine the incidence of intraop and PAR complications. In addition, demographics were obtained from the anesthesia record. For the purpose of this study reportable complications were listed as: hypertension, hypotension, dysrhythmia, nausea and vomiting, drug reaction, respiratory difficulty (major and minor), cardiac events and alterations in mental status. Defined criteria were used for each of the above complications. Intraoperative events were recorded by the anesthesia care team assigned to the case. PAR complications were recorded by the nursing staff. Data are expressed as percentage of mean ± standard deviation. Statistical analysis was performed using chi square and student t-test for unpaired data with $P < 0.05$ considered significant.

Results. (Table) The overall PAR complication rate was 15.5% (OR complication rate = 13.5%). Gynecologic and ophthalmalogic procedures were associated with the highest overall PAR complication rates, 36% and 26% respectively ($P < 0.01$). Of the patients who developed a PAR complication, those receiving a general anesthetic had a significantly higher incidence than those receiving regional anesthesia ($P < 0.01$). Nausea and vomiting were the most frequently occurring PAR complications, with an overall complication rate of 11.2% (389 patients). Gynecologic surgery accounted for 39% of all nausea and vomiting reported. In addition, patients having ophthalmic surgery had a PAR nausea and vomiting rate of 33%. Hypotension was seen in 0.4% (139 patients), while hypertension was observed in 0.8% (278 patients). From this group of PAR patients, there were 3 unscheduled intensive care admissions. These patients were admitted for the diagnosis of rule out myocardial infarction (ROMI). However, no patient sustained a postoperative MI. No cardiac arrests occurred. Patients who sustained a PAR complication had a 40% greater length of stay in PAR (145 min vs. 107 min, $P < 0.01$). Duration of anesthesia and ASA physical status did not impact on PAR complications (P = NS). Continued upper airway support was necessary in 1.6% of patients entering the ambulatory surgical PAR. Patients > 42 years of age had the highest OR complication rate, 67% ($P < 0.001$), while patients < 42 experienced the greatest percentage of PAR complications, 80% ($P < 0.001$). If intraoperative hypertension was present, there was a 1.6 times greater chance of developing a PAR complication ($P < 0.001$). However, intraoperative hypotension was associated with only a 0.9 times increases in the PAR complication rate.

Discussion. The data from this study identifies subsets of ambulatory surgical patients who are at a significantly increased risk for the development of PAR complications. In addition, specific intraoperative factors, i.e., anesthetic technique, type of surgical procedure (gynecologic and/or ophthalmic), and patient age are associated with an increased potential for the development of PAR complications. As in earlier studies, nausea and vomiting were the most frequently occurring complications occurring in the ambulatory surgical PAR.

Of note is the finding of the increased incidence of PAR complications occurring in patients who developed intraoperative hypertension (defined as a diastolic blood pressure greater than 110 mmHg). In addition, the need for continued upper airway (556 patients) was a previously unreported complication in this patient population.

Or data reveals that the complications occurring in the ambulatory surgical PAR setting are more diverse than previously appreciated. These results emphasize the necessity for vigilant monitoring of the ambulatory surgical patient during the PAR period.

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Table: Major PAR Complication
N = 3,477

Overall Complication Rate	15.5%
Nausea/Vomiting	11.2%
Upper Airway Support	1.6%
Hypertension	0.6%
Hypotension	0.4%

TITLE: ULNAR TRAIN-OF-FOUR AS A PREDICTOR OF FACE MOVEMENT DURING INTRACRANIAL FACIAL NERVE STIMULATION

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INTRODUCTION

Direct intracranial electrical stimulation of the facial nerve is used frequently in posterior fossa surgery to help identify cranial nerve roots.[1] A problem is uncertainty as to the degree of muscle relaxation that is compatible with both reliable face movement during intracranial facial nerve stimulation and patient immobility during a balanced anesthetic. Ulnar nerve stimulation with surface electrodes and observation of thumb adduction [train-of-four (TOF)] is used commonly to monitor neuromuscular blockade clinically, but whether TOF predicts facial motor response to direct intracranial stimulation is unclear. Accordingly, we evaluated the hypothesis that a high degree of motor blockade as assessed by ulnar TOF does not preclude satisfactory facial nerve monitoring.

METHODS

Six adult ASA I-II patients without facial nerve dysfunction scheduled for resection of small (< 2 cm) acoustic neuromas were studied. Each was lightly premedicated and anesthesia was induced with thiopental and fentanyl or sufentanil. Tracheal intubation was facilitated with succinylcholine. No additional relaxants were given and at least 2-3 h elapsed between succinylcholine and the start of the study. Anesthesia was maintained with nitrous oxide, isoflurane, and additional narcotics. Evoked facial and thumb movements were assessed by piezoelectric accelerometers. Accelerometry correlates closely with force-displacement transducer measurements.[2] One accelerometer was securely placed over the thenar eminence; the fingers wre taped firmly to a wrist board to prevent motion artifact. Surface electrodes were positioned over the ulnar nerve such that the distal positive electrode lay 5 cm proximal to the wrist crease. A second accelerometer was positioned over the patient's cheek ipsilateral to surgery at a point considered optimal for sensing both circumoral and circum-orbital movements.

Once the facial nerve was accessible, baseline recordings were obtained of facial and thumb responses to supramaximal stimulation. The facial nerve was stimulated intracranially by the surgeon with a 60-Hz constant voltage monopolar stimulator. The ulnar nerve was stimulated simultaneously with a standard 2-Hz constant current stimulator. After baseline measurements were obtained, the patient was given a bolus of atracurium (0.2-0.5 mg/kg). Ulnar TOF was assessed every 10 s and the facial nerve was stimulated at 5-min intervals for the duration of the study. Accelerometer responses were recorded on a strip-chart recorder. The anesthetist (who was unaware of accelerometer data) also observed the face and thumb for movement. The process was repeated until all four thumb twitches were present. Accelerometry data were analyzed at two points: reappearance of the first thumb twitch (point 1; approximately 90% block), and return of the fourth thumb twitch (point 2; about 70% block).

RESULTS

Facial movement evoked by intracranial facial nerve stimulation, assessed by accelerometry and simple observation, was well on the way to recovery before thumb twitches were detectable. The facial response recovered 12 ± 1.1 min (mean ± SEM) before thumb twitches were present. More importantly, when there was 90% block by ulnar TOF (point 1), facial movement was clearly observable and the accelerometer response had recovered to 76 ± 12% of baseline amplitude. When TOF showed 70% block (point 2), facial twitch had recovered almost completely (amplitude 87 ± 4% of baseline). Movement detected by the accelerometer was almost always apparent to the anesthetist.

DISCUSSION

Our data indicate that during recovery from a non-depolarizing block facial movement to intra-cranial stimulation of the facial nerve precedes return of the ulnar TOF and that TOF overestimates facial neuromuscular blockade. These data agree with a study[3] of the relationship between orbicularis oculi and adductor pollicis recovery from blockade in which the facial nerve was stimulated extracranially with surface electrodes. Factors such as preoperative facial nerve dysfunction secondary to compression, characteristics of the stimulus, and methods of monitoring could influence the results, however, so extrapolation to clinical conditions different from ours must be made cautiously. Nevertheless, this study provides a more rational basis for use of muscle relaxants during neurosurgical procedures requiring cranial nerve stimulation and suggests that reliable facial nerve monitoring is possible even in profoundly paralyzed patients.

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Title: BRAIN LACTATE AND NEUROLOGIC OUTCOME FOLLOWING INCOMPLETE ISCHEMIA IN HYPO-AND HYPERGLYCEMIC RATS

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Introduction. Reports indicate that elevated blood glucose during incomplete cerebral ischemia may worsen outcome by increasing brain lactate concentration (1). However, other studies have shown that hyperglycemia may reduce the size of cerebral infarction and improve outcome in models of hypoxia or ischemia (2). In these experiments we compared outcome following incomplete ischemia in rats treated by fasting, non-fasting and glucose administration to produce different blood glucose levels. An additional hyperglycemic group was treated with dichloroacetate (DCA) to stimulate pyruvate dehydrogenase, decrease brain lactate and possibly improve outcome from ischemia.

Methods. This research was approved by the Institutional Animal Care Committee. Male Sprague Dawley rats (350-450 g) were used. Rats were anesthetized, intubated and ventilated with surgical levels of isoflurane in oxygen. Catheters were inserted in the right femoral artery and vein for pressure recording and drug infusions and the subclavian vein for blood withdrawal. The right common carotid artery was isolated and a loose ligature placed around it for later clamping. At the completion of surgery the wounds were infiltrated with 0.5% bupivacaine and the inspired isoflurane concentration adjusted to 1.4% for a 30 minute equilibration period. Vecuronium was administered as needed to maintain paralysis and rectal temperature was maintained at 37 C.

Thirty minutes prior to induction of ischemia, hyperglycemia was produced in non-fasted rats by injection of 50% glucose solution (6 ml/kg ip). Fasted and non-fasted rats received 8% sodium chloride (6 mg/kg ip) to control for the osmotic load. A fourth group of rats received 50% glucose (6 mg/kg ip) followed 15 minutes later by an iv injection of 25 mg/kg DCA load 15 minutes before ischemia. Cerebral ischemia was produced by unilateral carotid ligation with hemorrhage induced hypotension to 30±2 mmHg and $FIO_2 = 0.2$. Arterial PCO_2 was maintained at 35-40 mHg by adjusting ventilation and normal pH was maintained by bicarbonate infusion. At the end of the hypotensive challenge the carotid artery was unclamped, the catheters removed, the incisions closed and the rat allowed to recover. Plasma glucose was measured at intervals during the control, ischemic and recovery periods. Neurologic deficits were initially evaluated 3 hours after recovery and repeated every 8 hours for 3 days. Scores were rated as follows: 0=normal, 1=paw adduction or abnormal posturing, 2=circling or rolling behavior marked by motor weakness or rigidity, 3= stimulated seizure activity, 4=unstimulated seizures, 5=death associated with signs of stroke. Neurohistopathology was scored on a scale of 0-4 by a blinded neuropathologist in 13 rats which survived the 3 day neurologic evaluation. Histopathology and neurologic outcome scores were correlated using a Spearman rank order correlation.

In a separate study, 4-5 rats from each test group were killed at the end of the ischemic period by microwave irradiation and regional brain tissue lactate concentrations measured in frontal cortex, parietal cortex, caudate, hippocampus and thalamus from both the ischemic and non-ischemic hemisphere.

Results. Fasted rats had blood glucose values of 79 mg% during ischemia and an average deficit score of 0.9, significantly better than glucose loaded rats (glucose = 496 mg%, deficit = 3.8) or DCA treated glucose loaded rats (glucose = 423 mg%, deficit = 3.6). Non-fasted (glucose = 292 mg%, deficit = 2.1) rats had blood glucose values and a deficit score higher than fasted but lower than glucose loaded rats. Neurohistopathology performed in rats which survived the 3 day testing period showed a significant correlation between deficit score and neuronal damage (r=0.77, p<0.05). Tissue lactate concentrations were similar in fasted, non-fasted and DCA treated glucose loaded rats but were higher in hyperglycemic rats.

Discussion. These results indicate that neurologic outcome is directly related to blood glucose concentration during ischemia but that brain lactate may not be the primary factor linking elevated blood glucose to a worsened outcome.

Table 1. Blood glucose, deficit score and tissue lactate in ischemic rats.

Group	n	Blood Glucose (mg%)	Deficit Score	Ischemic Cortex[a] Lactate (umol/g)
Fasted	8	79±7	0.9	7.48±.36
Non-fasted	8	292±28*	2.1	8.26±1.41
Glucose load	8	496±23*	3.8*	10.78±1.46*
DCA + glucose	8	423±29*	3.6*	8.89±.81

a = non-ischemic controls = 1.69 umol/g lactate

mean ±SE

* = P<0.05 compared to fasted using Mann-Whitney U test.

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Title: HEPATOCELLULAR INTEGRITY FOLLOWING PROLONGED I-653 AND ISOFLURANE ANESTHESIA IN SWINE

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Introduction: I-653 (CF_2H-O-CFH-CF_3) is a volatile anesthetic derived by fluorine substitution for the α-ethyl chlorine of isoflurane (CF_2H-O-CClH-CF_3). Lower solubility and the increased stability of I-653 provided by the strength of the C-F bond may result in less biotransformation of I-653 to potentially hepatotoxic metabolites. To test for hepatic injury, we measured plasma alanine aminotransferase (ALT) activity following prolonged anesthesia with I-653 or isoflurane in swine. Animals were anesthetized with and without the use of several additional drugs commonly used perioperatively in order to identify any hepatotoxic interactions of I-653 or isoflurane with these adjuvants.

Methods: This study was approved by the Committee on Animal Research of the University of California at San Francisco. All data are means ± S.D.. Eight female domestic swine (Group I, 15.9 ± 2.0 kg, about 10 weeks old) were anesthetized with I-653 for MAC determination and either isoflurane or halothane for surgical placement of aortic and pulmonary arterial cannulae. Each swine was placed in a padded sling 3 to 14 days (mean 6.6 ± 2.8) postoperatively for withdrawal of aortic blood samples prior to anesthesia. Anesthesia was then induced with I-653 or isoflurane in O_2 via a mask, and 2 mg/kg succinylcholine was given to facilitate endotracheal intubation. Each swine was anesthetized with I-653 or isoflurane in random order, 3-8 days (mean 6.0 ± 1.8) apart, for a total dose of 5.5 ± 1.0 MAC-hours of I-653 and 5.4 ± 0.3 MAC-hours of isoflurane. Anesthetic concentrations were varied in random order of 0.8, 1.2 and 1.6 MAC for I-653 and 0.7, 1.05, and 1.4 MAC for isoflurane. During the last 1 to 2 hours of anesthesia, these pigs were infused with increasing amounts of epinephrine from 0.2 to 4.0 μg/kg/min. Plasma samples were obtained immediately after, 4 hours after, and 3 to 8 days (mean 6.1 ± 2.1) after the anesthetic was discontinued. A second group of 5 swine (Group II, female, 16.8 ± 1.7 kg) received 9.7 ± 0.73 MAC-hours of each anesthetic on separate days during which they were successively given additional succinylcholine (1 and 2 mg/kg), N_2O (60%), fentanyl (50μg/kg bolus and 67μg/kg/min infusion or 100 μg/kg bolus and 134μg/kg/min infusion), naloxone (0.1 mg/kg), atracurium (0.6 mg/kg), thiopental (2.5 and 5.0 mg/kg), and a mixture of edrophonium (0.5 mg/kg) and atropine (0.005 mg/kg). Concentrations of these adjuvants used for swine were estimates of clinically relevant doses. For Group II, the concentrations of I-653 and isoflurane were maintained at 1.2 MAC throughout. Plasma was obtained before anesthesia, immediately after, 24 hours after, and 4 to 7 days (mean 5.8 ± 1.3) after discontinuation of the anesthetic. ALT activity was assayed at 30°C using a kinetic spectrophotometric determination of the oxidation of NADH at 340 nm and is expressed in International Units per liter of plasma (U/l). Data were analyzed by one-way ANOVA and two-way ANOVA with repeated measures, with the Newman-Keuls method of multiple comparisons. Statistical significance was accepted at $P < 0.05$.

Results: Plasma ALT activity in Group I pigs was not significantly different in samples drawn before anesthesia, at the end of anesthesia and 3 to 8 days after the first exposure for either anesthetic group (Table 1). ALT activity in samples drawn 4 hours after termination of anesthesia and concurrent epinephrine infusion was significantly lower than at other sample times for I-653 and isoflurane. The reduction in ALT levels was not significantly different between anesthetic groups. There were no significant differences between I-653 and isoflurane at any sample time for Group II pigs (Table 1).

Discussion: Increased plasma ALT is a sensitive indicator of hepatic necrosis or disturbances in liver cell permeability and often may be found before histological changes are detectable.[1] Following prolonged exposure to I-653 or isoflurane, there was no evidence of hepatic injury in the pigs we studied with or without the use of several anesthetic adjuvants. Some halogenated anesthetics (e.g., halothane) are known to cause liver damage in rare instances, possibly due to the formation of toxic metabolites.[2] Previous studies in rats[3] and eight of our swine[4] found that I-653 is metabolized less than isoflurane, which reportedly does not have hepatotoxic effects in clinical practice.[5] Liver tissue from enzyme-induced, hypoxic rats given I-653 and from rats repeatedly exposed to I-653 was free of histological signs of injury, such as swelling and necrosis.[6,7] Our data confirm these reports suggesting that I-653 is not hepatotoxic. The physical stability, resistance to biodegradation, low solubility, and rapid elimination of I-653 as well as the results of all toxicological studies to date support the prediction that I-653 will not cause hepatic injury if it is used clinically.

Table 1. Plasma Alanine Aminotransferase Activity

	Group I		Group II	
	I-653	Isoflurane	I-653	Isoflurane
Before Anes	27.0±9.1	27.9±8.2	29.9±4.3	31.6±14.4
End of Anes	24.1±5.2	27.3±8.8	26.2±4.3	26.6±13.7
4 Hrs Later	14.4±6.1*	11.0±8.8*	-	-
24 Hrs Later	-	-	24.2±3.3	23.0±6.7
3-8 Days Later	32.5±2.2	25.8±16.0	34.1±12.8	31.0±1.4

U/l plasma, mean ± SD
* = P<0.05 compared to other sample times with same anesthetic

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Title: EFFECTS OF HALOTHANE ON THE LENGTH-TENSION RELATIONSHIP OF ISOLATED MAMMALIAN VENTRICULAR CARDIAC MUSCLE

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Introduction. The pump function of the intact heart is influenced by end-diastolic volume and/or pressure, a phenomenon that is classically referred to as Frank-Starling's Law of the heart. Halothane decreased the slope of the end-systolic pressure-volume relation in the dog heart-lung preparation (1), in open-chest dogs (2), and in humans (3). The purpose of this study was to investigate the effects of halothane (H) on the length-tension relation of isolated ferret ventricular myocardium.

Methods. Nine papillary muscles from the right ventricle of adult male ferrets were mounted in a muscle chamber (30°C) filled with a physiological salt solution (mM): Na^+ 135, K^+ 5, Ca^{2+} 2.25, Mg^{2+} 1, Cl^- 103.5, HCO_3^- 24, $H_2PO_4^{2-}$ 1, SO_4^{2-} 1, acetate^{-1} 20, glucose 10, continuously bubbled with 95% O_2-5% CO_2 (500 ml/min). After stabilization, initial muscle length was set at L_{max}. In each muscle, the active force-length relationship was derived from isometric twitches (stimulus interval 4 seconds, voltage 10% above threshold) before, during, and after exposure to cumulative concentrations of H (from 0 to 1.5 MAC in 0.25 MAC increments) (4). After a steady state was reached and maintained for 10 minutes in each H concentration, isometric twitch contractions at respectively 100%, 96%, 92%, 88%, 98%, 94%, 90%, and 86% of L_{max} were recorded, in this order. These contractions were separated from each other by at least 7 isometric twitches at L_{max} to prevent time-dependent changes in developed force (5). For each muscle, and at each H concentration, a least squares error linear regression was performed relating the absolute value of DF to muscle length in % of L_{max}. Values of slope DF/%L_{max} were compared for differences at different H concentrations with repeated-measures analysis of variance. Pairwise comparisons between values of slope at control and at a particular H concentration were carried out with two-sided paired Student's t test. Differences were considered statistically significant when $P < 0.05$.

Results. Fig. 1 illustrates a typical example of force traces of 8 isometric twitches, each at a different muscle length, from L_{max} to 88.3% of L_{max} before (Fig. 1, left) and during exposure to 1 MAC H (Fig. 1, right). The amplitude of the twitch decreased with decreasing muscle length, both in control and in the presence of H. Fig. 2 shows the length-tension relation for 9 muscles (mean ± SD) in control and in the presence of 0.5, 1.0, and 1.5 MAC H. At each muscle length, developed force was decreased in a concentration-dependent fashion by H. In order to answer the question whether H decreases the length dependence of force development in cardiac muscle, the values of slope DF/%L_{max} of the length-tension relation of each muscle were analyzed as a function of H concentration, by means of least squares error linear regression. In each muscle, increasing the H concentration decreased the force-length relation slope DF/L_{max} ($P < 0.005$). Mean ± SD values of force-length relation slopes were plotted as a function of H concentration in Fig. 3.

Discussion. Recent insight into the effect of stretch on myocardial performance has revealed that the Frank-Starling mechanism has physiologic relevance in healthy human subjects (6). This study demonstrates that, for absolute values of developed force, this regulatory mechanism is attenuated by H in a concentration-dependent fashion in isolated mammalian ventricular muscle fibers. This anesthetic-induced depression of length-dependence of force development may result from anesthetic-induced reductions in calcium availability, and/or length-(6) and anesthetic-induced changes in calcium responsiveness of the contractile apparatus. Dr. Housmans was a Parker B. Francis Investigator in Anesthesiology for 1986. Supported by I.A.R.S., Puritan-Bennett Foundation, USPHS GM36365, Mayo Foundation. Dr. Baele was supported by the Foundation Saint-Luc, Belgium.

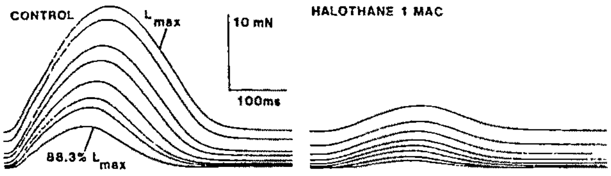

Figure 1

EFFECT OF HALOTHANE ON FORCE-LENGTH RELATION

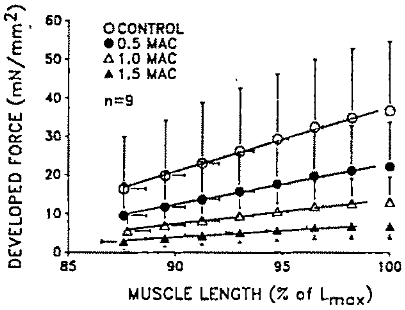

Figure 2

SLOPE OF FORCE-LENGTH RELATION

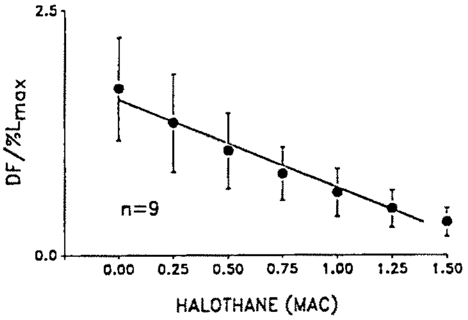

Figure 3

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Title: THE PERIPHERAL VASCULAR EFFECTS OF OXYTOCIN AND ERGONOVINE: A DOUBLE BLIND COMPARISON DURING GENERAL ANESTHESIA

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Introduction. Oxytocin and ergonovine are often used during general anesthesia and both exhibit cardiovascular side effects. Ergonovine in particular has been associated with a variety of cardiovascular emergencies in the parturient; they have been ascribed to the drug's peripheral vasoconstrictor activity(1). Despite the fact that these two agents are used interchangeably during general anesthesia, there has been no comparative study of their peripheral vascular effects. The standard method for investigating peripheral vascular drug activity in clinical pharmacology is venous occlusion plethysmography of the limb using a mercury strain gauge. This device measures forearm blood flow (FBF - ml blood/100 ml tissue/min) from which forearm vascular resistance (FVR - R units) can be derived. The aim of this study is to compare changes in FBF and FVR produced by oxytocin and ergonovine during general anesthesia. Patients undergoing evacuation of the uterus for first trimester spontaneous abortion were studied because of the inherent cardiostability of the procedure prior to test drug administration.

Patients. Following University Medical Research Ethical Committee approval, 20 ASA 1, consenting patients, 18-40 years were randomly allocated in a double-blind manner to one of two equal groups. Group OX was given oxytocin 500 iu and group ER was given ergonovine 500 µg IV during the operative procedure.

Methods. Anesthesia was induced with alfentanil 5 µg/kg and thiopental 3-5 mg/kg and maintained with 66% N_2O in O_2 with incremental (50 mg) thiopental as required. Patients breathed spontaneously via a face mask and Bain co-axial circuit. Potent inhalational anesthetic agents were not used because of their known peripheral vascular activity. The test drug was injected IV 5 min after induction of anesthesia. Then FBF and FVR were recorded at 1 min intervals for 5 min using the strain gauge, amplifier and recorder. Heart rate (HR - bpm) and mean arterial pressure (MAP - mmHg) were recorded at the same times using an automatic oscillotonometer on the contralateral arm.

Recordings of the 4 parameters (HR, MAP, FBF and FVR) were made 1 min prior to test drug administration to serve as control values. All measurements were made in the lithotomy position, and results were analysed by ANOVA and 2-tailed students 't' test for unpaired data.

Results. Patients were comparable with regard to age, weight and thiopental requirements. There were no statistically significant differences between the 2 groups for any of the 4 parameters in the control recordings prior to test drug administration. However, there were statistically significant differences between the 2 groups for both FBF and FVR at all 5 recording times after test drug administration ($p < 0.01$). The differences in FBF between the 2 groups were due initially to a transient rise in group OX and then due to a progressive decline in group ER. The reverse differences occurred with FVR (MAP/FBF) viz an initial fall in group OX followed by a progressive rise in group ER. Some of these changes are summarised in Table 1. The only statistically significant differences between the 2 groups in respect of HR and MAP occurred at +1 min relative to injection and were due to transient tachycardia and hypotension in group OX.

Discussion. These data indicate that oxytocin causes a sharp rise in FBF accompanied by short-lived vasodilation lasting 1-2 min. On the other hand ergonovine produces a progressive decline in FBF accompanied by sustained vasoconstriction. The vascular changes attributable to both drugs were accompanied by only minimal alterations in HR and MAP. These 2 drugs posess very different peripheral vascular profiles and the choice of agent should be determined by the cardiovascular status of the individual patient.

Table 1. FBF and FVR (mean ± SEM) before and after oxytocin (OX) and ergonovine (ER), given at time 0.

Time	FBF		FVR	
(min)	Group OX	Group ER	Group OX	Group ER
-1	4.3±0.2	3.8±0.3	21.1±1.0	24.5±2.2
+1	8.8±1.2*	3.5±0.3	10.5±1.9*	28.6±3.1
+3	6.5±0.5*	2.8±0.2	14.5±1.0*	37.4±5.4
+5	5.3±0.5*	2.5±0.2	18.0±1.6*	43.7±6.0

* $p < 0.01$ between groups OX and ER

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Title: **STRUCTURE OF THE THIRD CLINICAL YEAR OF ANESTHESIA RESIDENCY**

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Introduction: May 1988 marked the initiation of the third clinical anesthesia year for residency training ("CA-3") as required by the ABA for board eligibility. The ABA describes the goals for this year as "Advanced Anesthesia Training" and outlines guidelines for it as three different tracks: Advanced Clinical Track, Subspecialty Clinical Track, and Clinical Scientist Track. This abstract sumarizes the results of a survey designed to assess how these guidelines are being implemented.

Methods: In June 1988, surveys were distributed to all Chief Residents of anesthesia residency programs across the country attending the 1st Annual Chief Residents Meeting. They were instructed to indicate how their programs have structured the CA-3 schedule for the upcoming year. The results are reported as a percentage of programs completing the survey.

Results: Eighty-four (79%) surveys were completed and returned from 107 distributed. This represents 55% of the 152 anesthesiology residency programs within the US.

All programs responding offer the Advanced Clinical Track (advanced and comprehensive anesthesia assignments). Thirty-three (39%) are able to provide a 9-12 month Subspecialty Track. An additional thirty-four programs are able to offer at least one 6-month subspecialty rotation allowing fulfillment of the ABA Subspecialty Track via the alternative of two 6-month rotations. Thus, only sixty-seven (79%) of the programs offer the Subspecialty Track in at least one of the two forms, though the majority of programs plan shorter periods of subspecialty training for their residents during the CA-3 year. Fifty-eight (69%) programs offer the Clinical Scientist Track.

The subspecialty rotations offered include those subdisciplines listed in the ABA handbook: OB, peds, neuro, cardiac, ICU, pain, ambulatory, regional, and PACU.[1] In addition, several programs expect to offer rotations in vascular, trauma, ENT, lithotripsy, organ transplantation, and hyperbaric medicine. See Figure 1.

The number of subspecialty rotations offered at each program varies from one to twelve. The duration of the rotations varies from one to 12 months: although the preponderence of rotations are less than six months in duration. See Figure 2.

A majority of programs, 66 (79%), indicated that resident preference was the major determinant of CA-3 schedule assignments. Department preference guided the decision at 9 (11%) and the remaining 9 (11%) designed the schedule taking into account both department and resident desires.

Sixty-one (73%) programs allow residents to arrange an extramural rotation in selected subspecialties. Thirty-one of these programs allow residents to go elsewhere because they are unable to provide the requested rotation. Forty-seven (56%) of the programs indicated that residents taking extramural rotations would be financially supported by the home program.

Many programs encourage the residents to pursue research projects and thirteen (15%) of the programs have mandatory research requirements.

Discussion: The availability of the the three tracks outlined by the ABA is highly variable. Of the three ABA tracks, all programs report providing the Advanced Clinical Track. Although most programs have designed short subspecialty rotations, a lack of available clinical material have rendered many programs unable to offer 6 month or longer rotations for the Subspecialty Clinical Track. As a result, pursuit of fellowship positions is likely to continue. The Clinical Scientist Track is offered at 69% of the programs, yet many programs indicate that no residents requested this option for the coming year.

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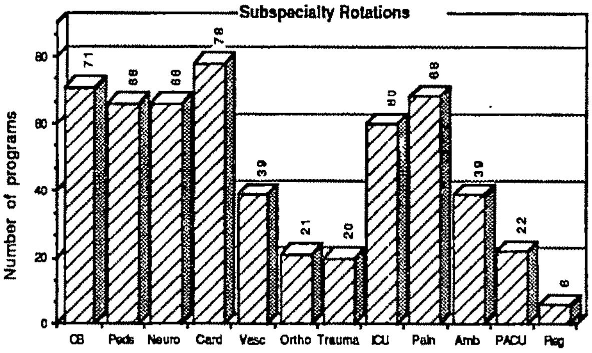

Figure 1. Number of programs offering each subspecialty.

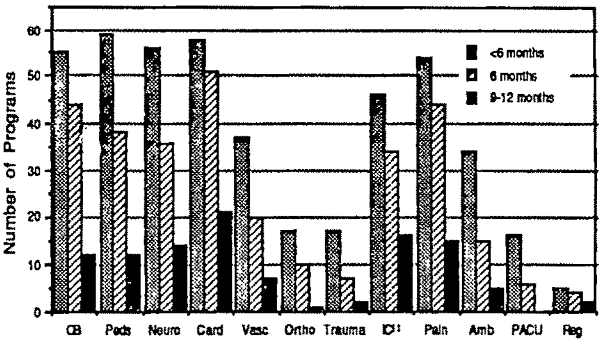

Figure 2. Subspecialty rotations and durations offered.

Title: DILEVALOL AS A HYPOTENSIVE AGENT DURING PROSTHETIC HIP SURGERY

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Introduction. The beneficial effects of a deliberate hypotensive anesthetic technique for prosthetic hip surgery are well established.[1,2,3] Reduced blood loss and improved operating conditions are well recognized advantages of this technique.

Several methods of reducing blood pressure during surgery are available. Dilevalol, an optical isomer of labetolol, is a new beta-blocker and has a dual mechanism of action, beta-adrenergic blockade and vasodilation through beta-2 agonist properties. This study was undertaken to determine the dose of dilevalol required for the induction and maintenance of controlled hypotension during prosthetic hip surgery as well as the duration of its action.

Methods. Fourteen patients (average age 61.2 years) undergoing total hip replacement suitable for a deliberate hypotensive anesthetic technique were studied. Institutionally approved informed consent was obtained during the pre-operative visit.

Exclusion criteria were: contraindications to beta-blockers, cerebrovascular accident or history of transient ischemic attacks, myocardial infarction within the last year, heart block greater than first degree, constrictive pericarditis, congestive heart failure, history of asthma, chronic obstructive pulmonary disease or any existing pulmonary disease and clinically significant renal disease (serum creatinine >1.5 mg/dl) Patients were premedicated with diazepam 0.15 mg/kg. General anesthesia was induced with sodium thiopental 3-5 mg/kg and tracheal intubation was facilitated with succinylcholine 1 mg/kg. Anesthesia was maintained with nitrous oxide and oxygen, fentanyl citrate 1-5 mcg/kg, and vecuronium bromide, 0.05-0.1 mg/kg, intravenously as required. Blood pressure was measured directly with an indwelling radial artery catheter. Urine output, blood loss and volume of intravenous fluid were measured. Baseline mean arterial pressure was recorded before the administration of dilevalol. The goal was to produce a 20% reduction in the baseline mean arterial pressure recorded after the induction of anesthesia. Dilevalol was administered intravenously as intermittent bolus injections at five minute intervals. The initial bolus was 25 mg, subsequent dosages were 50 mg and 100 mg until the desired level of hypotension was achieved. Hypotension was maintained with repeated IV boluses of dilevalol (25-100 mg). The cumulative dose of dilevalol did not exceed 600 mg.

Results. Results of the fourteen patients are outlined in the table. Ten of fourteen patients responded with a 20% reduction in mean arterial pressure with a mean cumulative dose of 333 mg (SD±103) of dilevalol. A mean dose of 235 mg (±182) was needed to induce hypotension. Thereafter a mean of 92.5 mg (±69) was required for maintenance of hypotension. The mean duration of the hypotension was 61 minutes (±49). Two patients did not respond after the maximum dose of dilevalol. Two other patients were eliminated from the study for the following reason: in the lateral position arterial blood gas analysis indicated the need for 100% oxygen necessitating the use of a potent inhalational agent. No complications resulted from participation in this study.

Discussion. Orally administered dilevalol has been well studied, but its usefulness intravenously for controlled hypotension has yet to be established. Intravenous dilevalol is easily administered and easily controlled, and in addition its duration of action is suitable for prosthetic hip surgery. Therefore, based on this preliminary data, we feel a larger scale study is warranted to determine the safety and efficacy of intravenous dilevalol for induction of controlled hypotension for prosthetic hip surgery.

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TABLE

Patient Number	Baseline MAP	Average MAP During Hypotension	Cumulative Dose	Duration
1	92mmHg	69mmHg	535mg	35 min
2	109	86	235	10
3	111	75	285	15
4	93	70	275	100
5	91	71	175	30
6	Eliminated			
7	97	74	375	35
8	89	70	375	25
9	109	82	400	105
10	81	66	400	150
11	No Response			
12	110	87	275	105
13	Eliminated			
14	No Response			

Title: ELECTRICAL VERSUS MECHANICAL ASSESSMENT OF NEUROMUSCULAR BLOCKADE DURING VECURONIUM INFUSION

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Introduction: Vecuronium(V) is a nondepolarizing monoquaternary muscle relaxant with an intermediate duration of action of approximately 25 to 55 minutes[1]. V appears to: a) have no effect on heart rate or blood pressure[3], b) lack accumulation on repeated doses[4], and c) be easily antagonized by anticholinesterases[2]. These properties make V infusion useful in patients requiring hemodynamic stability and ease of reversal. Neuromuscular blockade may be evaluated with adductor pollicis contraction (mechanomyography-MMG) or evoked electromyography in response to supramaximal stimulation. The reduction in EEMG response may be less than MMG depending on the relaxant used[3,4], so theoretically larger doses of relaxants might be given if EEMG is used. This study was undertaken to determine if this difference in response would cause different infusion for V.

Methods: This study was approved by the local ethics committee. Twenty ASA class I or II patients for were studied. Pre-medication was diazepam 5-10 mgm. Patients were taking no drugs known to interfere with neuromuscular transmission.

Patients were randomized for adjusting the infusion by EEMG (Group I) or MMG (Group II) although both monitors were applied. A Datex NMT-221 (Puritan-Bennett) EEMG device was attached as well as a force transducer (Medar APM) with with 300 grams of preload on the thumb. The apparatus was firmly fixed to the operating table.

Anesthetic drugs were thiopental (3-5mg/kg) and sufentanil (0.5-1 μg/kg) for induction and sufentanil infusion and nitrous oxide (2L/11) for maintenance.

After induction, the EEMG was calibrated and baseline values for train-of-four were recorded. V, 100 μg/kg was administered and the time for first twitch of train-of-four (T1) to equal 0 was recorded. V infusion was started at T1=25% and adjusted to keep T1=10%. V was stopped 30-45 minutes before the operation was completed and times were noted when T1=10%, 25%, 50%, 75%, and 100%. 4 μg/kg glycopyrrolate and 100 μg/kg pyridostigmine were administered at 25% recovery. Clinical assessment of recovery from neuromuscular blockade was judged by the ability to sustain hand grip and fifteen second head lift.

Between group differences were analyzed by two sample t-test; within group differences by one sample t-test.

Results: There were no significant differences between age, weight, dosage of V bolus or infusion, duration of infusion, duration of the intubating dose of V, or recovery index (25-75% recovery time).

T1 was significantly larger in EMG than MMG in both groups at the end of the intubating dose and during the maintenance infusion. The diffenerence failed to reach statistical significance during recovery.

Table (mean±SD)

	Group I(n=12)	Group II(n=8)
Age(yrs)	13-57	26-67
Weight(kg)	72.4±1.7	73±10.2
V bolus (μg)	735±207	564±357
Onset (min)	6.5±5.18	4±.577
Duration intubating dose(min)	40.1±1.1	39.6±1.5
V infusion (μg/kg/min)	2.08±1.08	1.33±.414
Duration of infusion(min)		
25-75% recovery time(min)	16.3±.1 (n=7)	15.6±0.09 (n=5)
Difference in % T_1 Recovery		
EMG minus MMG at 25% recovery (%)	21.6±11.1*	23.9±17*
EMG minus MMG at 10% recovery (%)	5±7.9	-2.1±9.3
EMG minus MMG at 2nd 25% recovery (%)	6±11.8	4±24.8
EMG minus MMG at 50% recovery (%)	9.4±2.1	2.9±37.6
EMG minus MMG at 75% recovery (%)	24.6±24.8	-6.25±58
EMG minus MMG at 100% recovery (%)	24.7±26.5	-47.2±67.2

* difference is significantly>0 ($p<0.05$)

Discussion: EEMG response is more resistant to V infusion than MMG early in the operation. This difference agrees with Epstein[5] who reported an approximately 15% difference between the two techniques. The mean V dosage tended to be higher in Group I than Group II, but wide interpatient responses prevented statistically significant differences in dosage requirements.

Two conclusions may be made from these results. First, the infusion rates must be individualized for each patient with the use of proper monitoring. Second, EEMG is more resistant than MMG to V infusion, but this does not cause a statistically significant change in dosage requirments.

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Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University

Title: PREGNANCY INDUCED NALOXONE REVERSIBLE ANALGESIA IN RATS

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Introduction. Although there is a general clinical impression that a parturient has a lowered requirement for "pain relieving drugs" human psychophysical tests of pain thresholds in pregnant females have not always supported the concept of pregnancy induced analgesia. Previous studies in experimental animals that have demonstrated pregnancy-induced and naloxone-reversible analgesia have also been challenged. Those studies, however, only assessed somatic stimuli. Relatively little attention has been given to visceral nociception, in spite of its obvious clinical importance. In our own pilot studies using a saline induced writhing test, endogenous visceral pain tolerance was noted prior to delivery. However, widely used visceral pain models such as writhing tests suffer from problems of reliability and reproducibility in pregnant animals. Recently, colorectal distension has been reported as a useful method for the quantitiative study of noxious visceral stimuli in rats. If pregnancy induced analgesia does occur an understanding of the mechanisms associated with its induction could provide new insight into pain management. The purpose of this study was to evaluate colorectal distension as an adequate stimulus for future studies of the physiology and pharmacology of pregnancy induced analgesia.

Methods. This protocol was approved by the Yale University Animal Care and Use Committee. Experiments were performed on unanesthetized female Sprague-Dawly rats (200-300 g), which were randomly divided into two (pregnant and non-pregnant) groups. Four tests were used to assess each animal's response to painful stimuli. Colorectal distension was induced by inflation with air of a 7 to 8 cm-long, pressure-monitored flexible latex balloon inserted intra-annally into the descending colon and rectum. Intracolonic pressure was continously monitored directly via in-line pressure transducer. Air pressure within the intracolonic balloon was steadily increased at a rate of approximately 5 mmHg/sec beginning at 0 mmHg. Unitl contraction of abdominal musculative was detected. The pressure required to induce contraction was defined as the threshold response. In analyzing writhing reactivity 1.5 ml of 4% saline was injected intraperitoneally and individual rats were scored over 3 min periods for the presence of characteristic changes in posture associated with writhing. Hot plate and tail flick thresholds were defined as the time required for the animals to withdraw from a radiant heat source focused on the foot or tail.

After determining the pain thresholds before pregnancy, one group of rats (n = 10) were mated and retested at day 7 and 21 of pregnancy and 1, 3, 5, and 7 days after parturition. Following testing on day 21, the animals received 1.0 ug/kg of naloxone and were retested. The other group of rats (n = 6) were mated but did not become pregnant and were tested in the same manner with the same interval between tests omitting day 5 and 7 of the "post-partum" period. Each test (except writhing) responses was repeated ten times each day and was spaced 30 seconds apart. The mean of the last five tests at each time point was used for analysis.

Results. As shown in Table 1 pregnant animals demonstrated a significant increase in threshold for colorectal distension, hot plate and tail flick 1 day before and 1, 3 days after parturition. The increased thresholds returned to pre-mated baseline by postpartam day 5. Naloxone significantly reduced the increase observed at day 21 of pregnancy. In contrast, the same pattern of alternations in pain thresholds during repeated testing over the same time span for the non-pregnant animals was not seen. As in pilot studies writhing responses were too variable to be analyzed.

Discussion. Qauntitative studies of visceral nociception have been limited due to lack of a reproducible visceral stimulus in pregnant animals. This study presents evidence that colorectal distension is a reproducible noxious visceral stimulus that can be used in studies performed in pregnant rats. Our data indicate that a naloxone reversible visceral tolerance is demonstrated late in pregnancy. Moreover, it extends into the early post-partum period. Naloxone reversability suggests the possible role of endogeous opiates. Of particular interest, pregnancy induced analgesia suggests a mechanism by which animals may enhance their tolerance of pain. An understnading of that process may provide better ways to manage pain in humans.

Supported by NIH NS-23033

				DAY 21 AFTER NALOXONE	POST-PARTUM		
	CONTROL	DAY 7	DAY 21		DAY 1	DAY 3	DAY 5
PREGNANT							
Col. Dist.+ (mm Hg)	25.9±3.1	26.5±3.8	34.9±2.9*	24.3±2.9^t	33.8±5.6*	32.3±6.0*	28.4±5.0
Hot Plate (sec.)	7.0±0.6	7.6±1.2	9.0±1.2*	7.0±0.9^t	9.3±0.9*	8.4±0.4*	7.3±0.5
Tail Flick (sec.)	5.1±0.6	6.2±1.2*	7.1±1.4*	5.0±0.7^t	5.8±0.4*	5.8±0.5*	5.3±0.6
NON-PREGNANT							
Col. Dist.+	24.0±3.1	22.4±2.3	22.5±2.4	22.9±2.8	24.9±4.7	23.2±3.2	-----
Hot Plate	6.7±0.5	7.0±1.1	7.4±0.8	7.4±0.3	7.0±0.4	7.1±0.4	-----
Tail Flick	4.8±0.3	5.3±0.2	4.9±0.2	4.7±0.4	5.2±0.4	5.1±0.4	-----

+Colorectal Distension
*Significant increase from pre-mate value * $p<0.05$
^{t}Significant reduction from Day 21 value ^{t} $p<0.05$
All values are mean ± SD.

Title: INTRATHECAL METHADONE 5MG AND MORPHINE 0.5MG FOR POSTOPERATIVE ANALGESIA: A COMPARISON OF THE EFFICACY, DURATION AND SIDE EFFECTS

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Introduction. Methadone is a lipid soluble opioid which is cleared from the CSF by rapid absorption into the spinal cord (1). Intrathecal methadone 1mg provides inferior analgesia and fewer supraspinal adverse effects than morphine 0.5mg and 1mg (2). In an attempt to determine whether larger doses of methadone can provide satisfactory and safe analgesia we compared the analgetic and adverse effects of intrathecal methadone 5mg with morphine 0.5mg (an effective and safe dose).

Methods. Twenty patients scheduled for total knee replacement, or total hip replacement were included in this study after institutional informed consent was given. The subjects were divided into 2 groups: 1) methadone 5mg (n=10), 2) morphine 0.5mg (n=10). The patients were randomly assigned to a treatment group and the drug was administered in a double-blind manner. Commercially available preservative-free morphine (Duramorph) 1mg/ml and methadone 10mg/ml were used, and all injectates were standardized to a volume of 1ml with sterile water. The opioid was instilled intrathecally at the end of the surgical procedure. No premedication or intraoperative opioid was given and systemic opioids were withheld until requested or deemed necessary in the postoperative period. Assessments commenced 1 hour after the subarachnoid injection and continued for 24 hours. The observations comprised a patient analysis of pain and/or analgetic effect using a rank pain score system and numerical pain rating out of 10. Adverse effects such as nausea, vomiting, urinary retention and respiratory depression were sought. Repeated arterial blood gas measurements were done. Statistical analyses were performed using the Wilcoxon's rank sum test on unpaired data and Fisher exact probability tests. $P<0.05$ was considered statistically significant.

Results. The median pain scores associated with morphine were consistently lower than with methadone ($p<0.05$) (Table 1). The time to the first analgesic supplement was significantly longer with morphine than with methadone ($p<0.05$) (Table 2). Considerably less morphine supplementation was required in the 24 hours after the intrathecal injection ($p<0.05$) (Table 3). Facial pruritus was unique to morphine (Table 4). Nausea and vomiting was more common with morphine (Table 4). Urinary retention was less frequently encountered with methadone but this was not statistically significant (Table 4). Respiratory depression was rare and evanescent in both groups (Table 4).

Discussion. Intrathecal morphine 0.5mg provided excellent analgesia of better quality and longer duration than methadone. Supraspinal side effects such as facial pruritus, nausea and vomiting were less frequently encountered with methadone than morphine. The inferior analgesia and fewer supraspinal adverse effects associated with intrathecal morphine may be a reflection of its avid binding to the spinal cord and unreliable rostral spread within the CSF to relevant spinal and/or supraspinal areas of the CNS. The hydrophilic morphine promotes both spinal and supraspinal activation of opioid receptors, which may be essential for the provision of superior analgesia.

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Table 1. Intrathecal Morphine vs. Methadone Median Pain Scores (Scale 0-10)

Hrs after Opioid Inj	Morphine 0.5mg	Methadone 5mg
1	0.5	0
2	0.5	0
3	0	0
4	0	1
5	0	3
6	0	4
8	0	3.5
10	0	5
18	0	3.5
24	0.5	3.5

Table 2. Time for First Analgesic Supplement (Hrs)

	Morphine 0.5mg	Methadone 5mg
Median	15	6.25
Interquartile Range	13.5-27.25	4.25-9

Table 3. Supplementary Morphine Dose (mg) in First 24 Hours

	Morphine 0.5mg	Methadone 5mg
Median	5.5	23
Interquartile Range	0-24	9-33

Table 4. Adverse Effects

	Morphine 0.5mg	Methadone 5mg
Pruritus	6/10	6/10
Facial Pruritus	6/10	0/10
Nausea/ Vomiting	6/10	1/10
Respiratory Depression $PaCO_2 \geq 50mmHg$	2/10	2/10
Urinary Retention requiring catheterization	6/7	5/9

Title: DOES SINGLE BOLUS ESMOLOL 2 MINUTES BEFORE INTUBATION PREVENT TACHYCARDIA?

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Introduction: Rapid control of rise in heart rate and blood pressure during surgery is critical, especially for patients with pre-existing coronary artery disease. At stress of induction and intubation, catecholamines may increase heart rate (HR) and systolic blood pressure (SBP). The purpose of this study was to determine if bolus esmolol (E), an ultra short acting and rapidly eliminated beta blocking agent, would blunt these effects.[1] Bolus E has been used in doses up to 300 mg.[2] The objectives of the study were to: (a) determine an effective dose of bolus E which would prevent intubation induced cardiovascular stress and (b) determine an optimal dosing interval prior to intubation for an effective response.

Methods: Institutional board approval was obtained and informed consent from each patient was signed. Forty patients were studied and divided into four equal groups: 1. placebo; 2. E, 50 mg; 3. E, 100 mg; 4. E, 150 mg. The design of the investigation was randomized, parallel, open label and placebo controlled. We included ASA 2, 3, and 4 male patients over 21. No patient was used with a cardiac condition which would, in the investigators' judgement, reduce the interpretability of study variables; these included sick sinus syndrome, etc. and asthma. E was diluted to 10 mg/ml and the placebo vehicle diluted in the same volume. The heart rate was continuously recorded by lead V 5 EKG and the blood pressure either by a radial catheter or self inflating pressure recorder (Accutorr, Datascope). HR was recorded every 15 sec and SBP every min during baseline and from the administration of thiopental until 6 min after intubation. Vital signs were then recorded each 5 min until 20 min elapsed. All patients were premedicated IM 30-60 min before anesthesia with midazolam 0.03 mg/kg, meperidine 1.0 mg/kg and glycopyrrolate 0.2 mg. After 3 min of baseline recordings, 5 mg/kg thiopental IV were administered at time zero followed by E and then succinylcholine 1.0 - 1.2 mg/kg. A mean period of 2 min elapsed between E and before relaxation, laryngoscopy and intubation. Patients were maintained on N_2O 60% in O_2 and isoflurane at an average concentration of 1 MAC plus 10%. Controlled ventilation was instituted and the ET_{CO2} was kept between 30-35 mm Hg. Any adverse experiences such as bradycardia (< 50 bpm), hypotension (< 90 mm Hg systolic) or bronchospasm were recorded. Analysis of variance was used to compare the four treatment groups at each study time with the use of baseline HR and SBP as a covariant. If significant ($P < .05$) differences were found, treatment differences were determined using least squares adjusted means.

Results: Figure 1 is a plot of the mean % HR ± SE change from baseline against time and events over a 6+ min period. There is an increase in HR of 5-15% following thiopental administration. At intubation, a rise in HR was seen for all groups, but this was lowest for 100 and 150 mg. No statistical significance was seen at any time or event between groups throughout the study period. There is a dose response effect. The 100 and 150 mg groups have the least % change in HR after intubation. The low statistical power, due to the small number of patients in each group may account for the lack of statistical significance. There is no difference between 50 mg and placebo. Change in SBP between groups was insignificant after intubation. No adverse effects were seen with any patient.

Discussion: Esmolol is a short acting beta blocker with a 2 min distribution and a 9 min elimination half life. It appears as though 2 min or less must elapse after esmolol administration and intubation. Further, a dose of 100-150 mg or more may have to be given for effect. The kinetics of esmolol dictate that single bolus administration has an extremely short effective period of action. Those bolus doses of E which protected against more than a 5-15% rise in HR after intubation in this study were ineffective in lowering maximal SBP compared to placebo. On the basis of this investigation we suggest that an E dose of 150 mg be used within 2 min of intubation if one is to expect any protection against tachycardia. No adverse side effects including bradycardia, hypotension or bronchospasm were seen with E. However, the advantage of E is that should any problem occur, the effect of this beta blocker would be dissipated in 10-15 min, an advantage compared with all other beta blockers.

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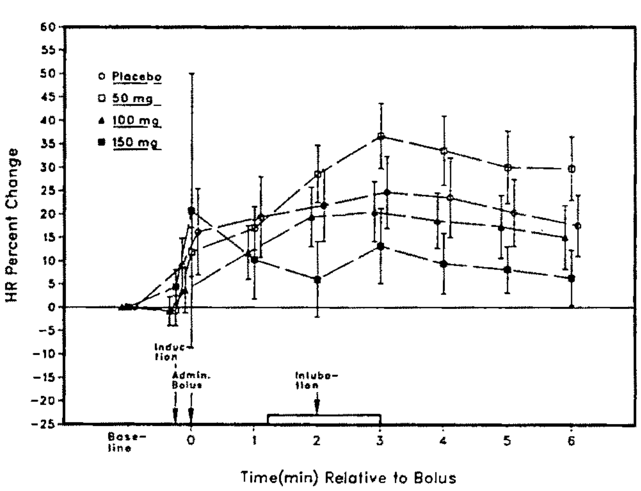

Title: ESMOLOL BOLUS BEFORE ANESTHETIC INDUCTION FOR TACHYCARDIA-HYPERTENSION

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Introduction: At anesthetic induction, thiopental and succinylcholine followed by laryngoscopy and intubation cause an increase in heart rate (HR) and systolic blood pressure (SBP). This study was designed to evaluate intravenous bolus esmolol (E), a rapidly acting and dissipating beta blocker as an effective pretreatment of this undesirable physiologic stress. Bolus E has been used in humans up to 300 mg IV. [1]

Methods: We obtained institutional board approval and signed informed consent from the 50 patients investigated, and divided them into 5 equal groups: a) placebo; b) E., 50 mg; c) E., 100 mg; d) E., 150 mg; and e) E., 200 mg. The investigation was randomized, open label and placebo controlled. Males were included who were ASA 2, 3, and 4. All patients were excluded with asthma or a cardiac condition which would, in the investigators judgement, make the interpretation of study variables difficult. E was diluted to 10 mg/ml and the placebo consisted of the E vehicle diluted to the same volume. HR was continuously recorded by lead V 5 EKG as was the SBP either by intra-arterial radial catheter or self inflating blood pressure mechanism (Accutorr, Datascope). HR was recorded every 15 sec and SBP every min for 3 min during baseline and from the administration of E for 8 min; then every 5 min for 20 min.

All patients were premedicated IM 30-60 min before anesthesia with midazolam 0.03 mg/kg, meperidine 1.0 mg/kg and glycopyrrolate 0.2 mg. After baseline, the placebo or E was administered, followed 90 sec later by thiopental 5 mg/kg IV and then succinylcholine 1.0 mg/kg. Laryngoscopy and intubation were performed approximately 4 min after the injection of E. N_2O 60% in O_2 plus isoflurane at approximately ED 95 were given by ventilator to maintain ET_{CO2} at 30-35 mm Hg. Any adverse experiences including bradycardia (< 50 bpm), hypotension (SBP < 90 mm Hg) or bronchospasm were recorded.

Analysis of variance was used to compare the 4 treatment groups at each study time with the use of baseline HR and SBP as a covariant. If significant (P > .05) differences were found, treatment differences were determined using least squares adjusted means.

Results: Figure 1 is a plot of the % change in HR from the administration of E over the next 8 min. All 5 groups dropped approximately 10 to 20% at 2 min which is the time of administration of succinylcholine. The placebo and 50 mg E dropped the least. The 150 and 200 mg groups decreased HR the most followed by a rise in HR ranging from -10% (E., 200 mg) to +20% (placebo). After intubation there is a rise in HR to 20-30% above the baseline level in the placebo, 50 and 100 mg E groups. The 150 and 200 mg E groups increased and remained at only +5 to +10% (p > 0.05). A dose response effect is seen. The change in SBP over the same time period demonstrated no significant differences among the five groups.

Discussion: E infusion has been used successfully as prophylaxis at induction to prevent intubation tachycardia and hypertension. [2] The kinetics of single bolus E suggest that a peak is reached at 2 min after IV administration and this is maintained briefly. Administration of bolus E 3-4 min prior to intubation appears to be too early. However, there is a dose response effect. Esmolol is a very short acting beta blocker with a 2 min distribution and a 9 min elimination half life. Not only must it be administered in proper dosage but also at the proper time to prevent intubation tachycardia and hypertension. On the basis of this investigation, we think an E dose of up to 200 mg 90 sec before thiopental is too early to protect against rise in HR and SBP; but the larger the dose the greater the effect. No adverse experiences such as bradycardia, hypotension or bronchospasm were seen. We conclude that this is a safe technique, but that E should not be given before induction.

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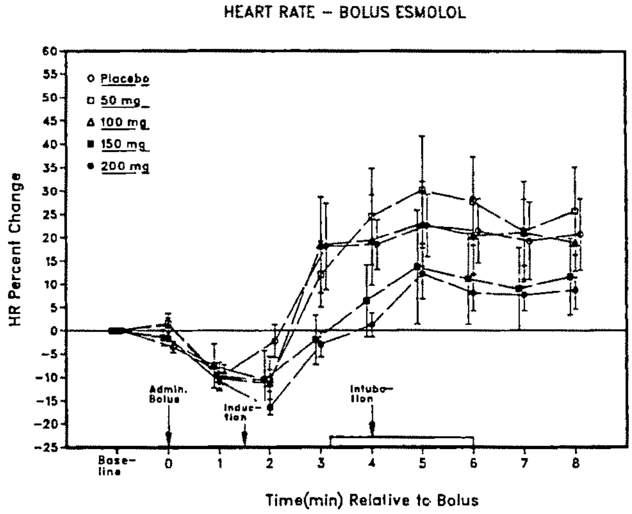

TITLE: BLOOD ETHANOL LEVELS FOLLOWING CELIAC PLEXUS BLOCK WITH 50% ETHANOL

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Introduction: Celiac plexus block with an alcohol solution is a recognized modality for the management of intractable upper abdomen pain in patients with malignancies. After this procedure, we have observed that patients often have the odor of alcohol "on their breath." Since these patients often are receiving multiple analgesic agents, we became concerned regarding the possible systemic effects of the ethanol, particularly when given in combination with other drugs such as opioids. These concerns are magnified by the fact that many of these procedures are performed on outpatients who then may leave the pain clinic while under the influence of multiple CNS depressants. This study, therefore, was initiated to examine the impact of celiac plexus block with alcohol on blood ethanol levels in patients with chronic pain.

Method: The subjects were 16 adult patients referred to us for nerve-block management of upper abdominal pain due to cancer, either as inpatients or during visits to our out-patient clinic. All patients had complete medical, surgical and neurological evaluations, and tumor location and extent was documented by CT or MRI scan. All patients were receiving opioid analgesics, either alone or in combination with non-opioid analgesics. Informed consent was obtained from each patient prior to celiac plexus block. A 500-1000ml infusion of crystalloid solution was given IV prior to the procedure.

Celiac plexus blockade was performed under CT scan control using 22 gauge needles of 17.8 cm length, introduced with the patients in the prone position. The tips of both needles were located just anterior to the body of the first lumbar vertebra with their placement confirmed by injection of radiopaque dye. On the left side, a transaortic approach was employed, with the needle tip crossing the anterior wall of the aorta.

Once satisfactory location of the needle-tips had been achieved, 2ml of 1% Lidocaine was injected slowly in order to reduce pain during the subsequent neurolytic block. 2 minutes thereafter, 25ml of 50% alcohol solution was slowly injected bilaterally. Blood samples for alcohol levels were drawn at 5, 15, 30, 60 minutes in all patients. 2 of the patients also had blood alcohol levels determined at 90 and 120 minutes. Patients were under constant observation for 60 minutes following alcohol block, with vital signs recorded every 15 minutes. No episode of clinically significant hypotension or any other complication was observed.

Results: Virtually all patients experienced pain relief. In addition, either a feeling of euphoria or an odor of alcohol on the breath was noted within 15 minutes of celiac plexus block. The figure summarizes the alcohol blood level data in the first hour after celiac block. No patient's blood alcohol level reached the legal limit for intoxication and, indeed, no patient became inebriated or sedated following the procedure. By 90 and 120 minutes post block, 2 patients had blood alcohol levels of only 13.5 gm dl 10^{-3} ± 6.4 SD and 16.0 gm dl 10^{-3} ± 2.8 SD, respectively.

Discussion: Celiac block is often performed as an out-patient procedure at our hospital. These data indicate that this procedure can be performed safely in outpatients, without undue concern for delayed synergistic CNS depression from systemic analgesics or other sedative medications as long as 50% ethanol solution is employed. Greater concentrations, however, may produce higher blood levels and possible systemic effects. Accordingly, we believe these patients should be monitored for more than one hour following the procedure. In the event that undue sedation develops in the post-block period, the clinician should consider that alcohol intoxication might be the cause, but that this may also be the result of the well-recognized cardiovascular effects of celiac plexus block.[1]

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Figure

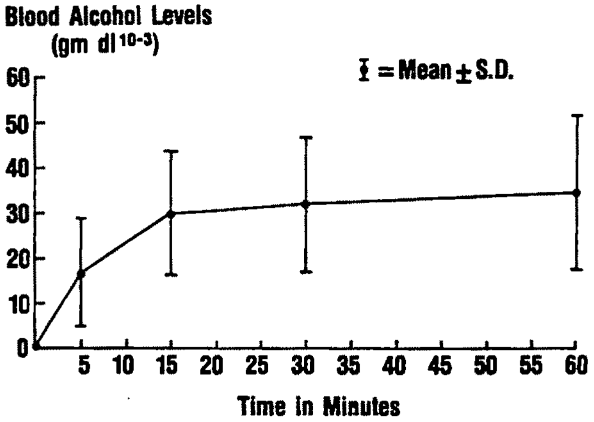

Figure: Time-course of blood alcohol levels following celiac plexus block with 50% ethanol solution.

TITLE: **MANAGEMENT OF REFLEX SYMPATHETIC DYSTROPHY PAIN: PARAVERTEBRAL LUMBAR SYMPATHETIC BLOCK VERSUS CONTINUOUS EPIDURAL BLOCK.**

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Introduction: Paravertebral lumbar sympathetic block is an accepted approach to the treatment of unilateral reflex sympathetic dystrophy of the lower extremities. However, this treatment usually entails multiple needle insertions at regular intervals. There is also a risk of inadequate pain relief due to incomplete sympathetic blockade. Moreover, congenital anatomical variations in the laterality and the extent of the sympathetic outflow, as well as derangements of anatomy due to previous trauma or surgery, may combine to limit the effectiveness of the conventional paravertebral approach. In light of these limitations the authors undertook this study to evaluate the efficacy of continuous epidural blockade for treatment of chronic reflex sympathetic dystrophy of the lower extremities.

Methods: The subjects of this study were seven patients (mean age 34 years, range 14-55) with reflex sympathetic dystrophy refractory to conventional unilateral paravertebral sympathetic block. All patients had had fair results using lumbar sympathetic blocks in the past, but the quality of their pain relief had deteriorated as indicated by increasing severity of pain as recorded by a visual analog scale, where 0 = no pain and 10 = the worst pain ever experienced.

Under fluoroscopic control a lumbar epidural catheter was placed with its tip located at the T8-T10 level. Proper position of the catheter tip was confirmed by epidurography with radiopaque contrast medium. In 5 patients 1% lidocaine solution (8-15ml) was injected via the epidural catheter three times daily. The remaining 2 patients were treated by continuous infusion of 0.5% lidocaine at a rate of 10-20 ml/hr. In all patients the period of treatment ranged from 4-14 days (mean = 8 days). A total of 11 catheter placements were performed, with replacement necessitated in 3 instances by catheter dysfunction.

Treatment was terminated based on successful amelioration of symptoms. At the beginning and again at the end of epidural block, pain severity was assessed using the visual analog scale. Pain relief was quantitated by the reduction in pain severity as recorded on the visual analog scale, and compared with the same data previously obtained before and after lumbar sympathetic blocks. Statistical comparisons were performed using Student's t-test for paired data. $P<.05$ was regarded as significant.

Results: No patient sustained toxic, neurologic or infectious complications from this therapy. In follow-up examinations for up to 21 months (mean duration = 10 months), the mean decrement in visual analog pain scale after epidural block was 6.6 ± 0.9 SE. In contrast the mean decrement following repeated lumbar sympathetic blocks was 2.6 ± 1.1 SE, $P<.05$. The duration of pain relief following epidural block ranged from 6-28 weeks (mean = 13).

Discussion: Based on these data, we believe that long-term epidural blockade affords better relief of reflex sympathetic dystrophy symptoms of the lower extremities than can be achieved by intermittent lumbar paravertebral sympathetic block. Not only is the latter uncomfortable, but repeated injections may be less well-tolerated by patients, particularly if a t.i.d. schedule is employed. Furthermore, the hazards of repeated deep nerve blocks are not inconsiderable. By contrast, epidural blockade can be achieved safely with the introduction of a single needle and catheter and can be readily repeated over a period of weeks. We conclude that this modality should be considered as an effective therapeutic alternative for the management of reflex sympathetic dystrophy.

Title: RECTAL pH IN CHILDREN

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Introduction. Recently published data suggest that rectal absorption of drugs is in accordance with the pH partition hypothesis [1] and thereby a function of rectal pH [2]. While pH in the rectum of adults is reported to be in the range of 6.8 - 7.9 no such data exist for children.
We have measured rectal pH in neonates, infants and children and investigated any possible dependence on sex, age and nutrition.

Methods. Following institutional approval and informed parental consent the study was carried out on 100 children (ASA 1) presenting for minor elective surgery. A further 8 children from the pediatric intensive care unit requiring artificial ventilation and total intravenous alimentation (TIVA) were investigated. Rectal pH was measured in the morning between 6 and 8 a.m. by one of the authors. Measurements were peceded by digital examination of the rectum and carried out only when the ampulla was free of faeces. Following a daily calibration procedure, all measurements were performed with the same monocrystal-antimony pH catheter (pH METER SYN-02 ᵀᴹ, Synectics AB, Stockholm, Sweden). The tip was positioned at a distance of 2 cm proximal from the anal sphincter and the reading was taken after a dwell time of 1 min. Under these conditions the device has an accuracy of ± 0.1. pH data were analyzed for dependence on gender, age and nutrition. Allocation by age was to three groups: neonates (≤ 4 weeks), infants (> 4 - 52 weeks) and children (> 52 weeks, ≤ 14 years) and by nutrition to 4 groups: "TIVA", "breast/bottle", "pap" and "mixed-food".
Statistical analysis was by Kruskal-Wallis (KW) and Wilcoxon (W) two-sample tests; p values (p_{KW}, p_W) were determined.

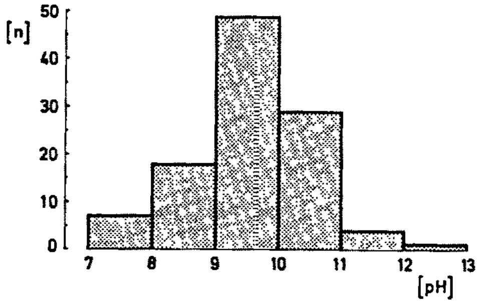

Figure 1: Distribution of rectal pH values.

Results. 30 girls and 78 boys were studied (78 children, 26 infants, 4 neonates; 8 TIVA patients, 22 breast/bottle (2/20), 24 pap and 54 mixed-food). Rectal pH was 9.6 ± 0.9 (mean ± S.D., range 7.2 - 12.1; Fig.1).
No difference was found with respect to sex (p_{KW} 0.1582) or age (p_{KW} 0.1152). Differences were noted between nutrition groups (p_{KW} 0.0048). The pH in the TIVA group was lower than in breast/bottle (p_W 0.00274), pap (p_W 0.022) and mixed-food (p_W 0.0005) groups. No differences were found between the latter three groups.

Discussion. Rectal induction of anesthesia was pioneered by Pirogoff in 1848 and currently enjoys a renaissance in pediatric anesthesia. Although pH is a recognized factor in absorption [3] it has so far received little attention. Our results show that rectal pH in the investigated age group is 9.6 ± 0.9, when measured 2 cm proximal from the anal sphincter. An empirical range including 95% of all rectal pH values in this age group would range from 7.3 to 11.8. pH appears to be largely independent from gender and age although some of the subgroups are too small to substantiate this. With respect to nutrition, pH was lower when no enteral digestion took place. However, rectal pH in children was found to be considerably higher than in adults. This unexpected alkalinity is possibly maintained by active secretion of bicarbonate from the rectal mucosa [4].
We conclude that rectal pH in children is higher than in adults and that this should be taken into account when drug formulations for rectal administration in children are considered.

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TITLE: A COMPARISON OF THE VASODILATING EFFECTS OF HALOTHANE AND ISOFLURANE ON THE ISOLATED RABBIT BASILAR ARTERY

AUTHORS: Niels F. Jensen, M.D., Michael M. Todd, M.D., David J. Kramer, B.A., Bruce A. Bollen, M.D., David S. Warner, M.D.
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Introduction. The effects of intravenous anesthetics and vasoactive compounds on isolated cerebral vessels have been well studied, but there is little information regarding the effects of volatile anesthetics. This is largely the result of difficulties associated with controlling the concentrations of volatile anesthetics in tissue baths; a problem we believe has been solved with the method described here (1). Using this system, we have conducted what we believe is the first comparative dose response study of volatile anesthetic-mediated relaxation in isolated cerebral vessels.

Methods. 22 NZW rabbits were studied. After a lethal dose of pentobarbital, the brain was removed from the skull and the basilar artery (BA) identified and removed. The left midline ear artery (EA) was also dissected free. The distal 8.0mm of the BA (o.d. 500μm) was divided into 2 equal segments, as was the distal 6.0mm of the EA (o.d. 1.0mm). Each of the 4 arterial segments was threaded onto a rigid clip and attached to a tension transducer in a sealed plexiglass perfusion chamber. The 4 separate vessel chambers were continuously supplied with 37°C buffered, protein free perfusate (ISM-pH 7.33-7.44), from a sealed, warmed, water-jacketed column continuously filled from a reservoir. 95% O_2/5% CO_2 flowing through calibrated anesthetic vaporizors (≈800ml/min) was bubbled through the columns to saturate the perfusate with O_2, CO_2, and, when desired, a controlled concentration of volatile agent. Perfusate was pumped into the chambers at a rate of 4ml/min (no recirculation).

Each of the segments was perfused with ISM for 30 min with no tension applied. The BA segments were then stretched to 1300 dynes and the EA to 1500 dynes. They were then constricted by changing the perfusate from ISM to one containing 30mM K^+ (ISK-30). Beginning 30 min later, the vessels were exposed to 15 min pulses of halothane or isoflurane in doses of ≈0.5, 1.0, 1.5, and 2.0 MAC, with a 30 min period of perfusion with anesthetic-free ISK-30 between each dose (order randomized) [Halo 1 MAC-1.39%, Isof 1 MAC-2.05%]. Volatile agent concentration in the bath was directly measured by GC, and the relationship between bath concentration (re-expressed as MAC-fraction) and relaxation was determined.

Results. Dose-response data for the BA is summarized in the Figure. Both halothane (Halo) and isoflurane (Isof) produced a dose-related reduction in BA tension, but there were no statistical differences between the two agents. Both drugs also resulted in statistically indistinguishable dose-related reductions in EA tension (not shown). However, the EA showed a steeper dose-response curve than that seen in the BA.

Discussion. Several studies have shown that Halo produces greater increases in cerebral blood flow (CBF) than does Isof (2). This has been interpreted as indicating that Halo is the more potent cerebral vasodilator. However, it has been suggested that the relative effects of the two agents on brain metabolism may play a role in determining their flow effects (3), and it is probable that vascular, metabolic, hormonal, neuronal, and other influences, all interact to control CBF. This study suggests, in a preliminary manner, that the effects of Halo and Isof on one component of this mixture - cerebral vascular smooth muscle - are, in fact, very similar.

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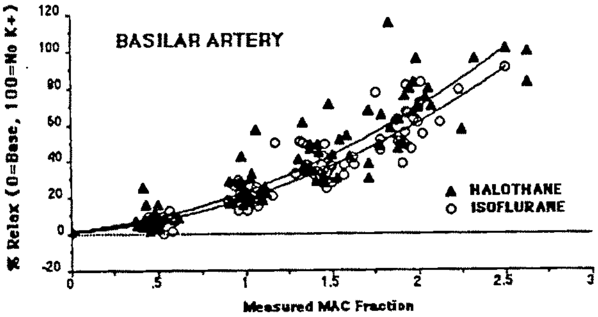

Legend. BA relaxation plotted vs measured MAC fraction in the vessel bath. These lines shown can be described by the following equations (Growth Curve Analysis).

Halothane: $Y-1.73+(9.24\ X) \div (12.33\ X^2)$, $r-0.891$
Isoflurane: $Y-1.04+(6.95\ X) - (11.58\ X^2)$, $r-0.922$

There are no intergroup differences. Note: 0% relaxation equals "Baseline," while 100% represents the tension measured prior to K^+ constriction.

Title: EFFECT OF INTRAVENOUS DROPERIDOL UPON NAUSEA AND RECOVERY USING ALFENTANIL ANESTHESIA

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Introduction. Alfentanil is a short acting narcotic particularly suitable for short duration outpatient surgery. Recovery is rapid from alfentanil-based anesthesia (1). A significant drawback of alfentanil-based anesthesia is a high incidence (45%) of nausea and vomiting (N/V) (1). Studies have demonstrated that using droperidol in association with alfentanil-based anesthesia markedly reduces the incidence of post-operative N/V (2). However, the question is raised as to whether the use of droperidol might significantly prolong the recovery period and therefore abolish one of the advantages of alfentanil. Here we examined the effect of different commonly employed doses of droperidol on the incidence of post-op recovery in a double blind fashion using a standard alfentanil-based anesthetic.

Methods. After approval by the Human Use Committee, 60 normal adults (ASA class I or II) who were scheduled to undergo short surgical procedures requiring general anesthesia were included in the study on a consecutive basis. The subjects were assigned randomly in a double blind manner to 3 groups of 20; 1) control-normal saline, 2) droperidol 0.01 mg/kg, or 3) droperidol 0.02 mg/kg. All study solutions were prepared and randomized by the hospital pharmacy in identical volumes. After giving informed consent, the patients were brought to the operating room, and IV placed and standard monitors applied. Anesthetic induction consisted of vecuronium 0.01 mg/kg, thiopental 3-5 mg/kg, alfentanil 25 µg/kg, and succinylcholine to facilitate intubation. Anesthesia was maintained with O_2/N_2O 30%/70% alfentanil 0.25-2 µg/kg/min and isoflurane .25 vol%. A nasogastric tube was placed after induction to evacuate gastric contents and removed with suction prior to extubation. Muscle relaxation was maintained with vecuronium and reversed with edrophonium and atropine. Immediately post-induction, a syringe containing one of the study solutions was given IV push. In the post-anesthesia recovery room (PARR), all patients were scored according to the Aldrete score noting the time to a score of 10 (3). Presence or absence of N/V was noted. A Trieger dot test was performed by every patient; 1) pre-op, 2) at the time of an Aldrete score of 10, and 3) upon discharge from PARR to further assess psychomotor recovery (4). The data collected was analyzed statistically using analysis of variance and χ^2 analysis.

Results. There was no statistical difference between each group's patient characteristics, anesthetic dose or duration per Table 1A. The incidence of N/V for control, 0.01 mg/kg, 0.02 mg/kg groups was 40%, 25% and 5% ($p < .05$) respectively. The time to Aldrete score of 10 and time to discharge are in Table 1B. The Trieger dot scores to evaluate psychomotor skills are in Table 1C. Statistical treatment of the recovery times and scores showed no statistical difference between the groups.

Discussion. 1) Droperidol 0.02 mg/kg given prophylactically during alfentanil-based anesthesia reliably diminished the incidence of N/V. 2) There appears to be a dose response effect of prophylactic droperidol upon N/V with 0.02 mg/kg being most effective. 3) Droperidol 0.02 mg/kg or 0.01 mg/kg does not appear to appreciably increase recovery time or psychomotor recovery compared to normal saline. These findings are consistent with most studies of prophylactic droperidol given to prevent N/V associated with other general anesthetics; although, only low doses such as given in this study have such negligible effects on recovery scores.

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Table 1:

	Normal Saline	0.01 mg/kg Droperidol	0.02 mg/kg Droperidol
A: Patient Characteristics (mean)			
Age (yrs)	34	34	32.5
Weight (kg)	68	67.45	67.45
Total Alfentanil (µg)	5374	4280	5568
Duration of Anesthetic	91.5	106.5	101.5
B: Recovery Times (min)			
Time to Score 10			
mean	25	15.25	25
range	(0-45)	(0-45)	(0-45)
Duration PARR Stay			
mean	54.2	58.5	56.75
range	(30-120)	(30-120)	(30-95)
C: Trieger Dot Scores (mm missed)			
Δ from Pre-op to Score 10			
median	10.5	24	17.5
(.25-.75)	(6-32)	(14-40)	(7-27)
Δ from Pre-op to PARR Discharge			
median	5.5	13	9.5
(.25-.75)	(1-15)	(4-17)	(3-18)

Title: CONTINUOUS COMPUTERIZED PULMONARY VENOUS ADMIXTURE FROM HEMOGLOBIN SATURATIONS EVALUATED IN A PIG MODEL

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Introduction. Calculation of pulmonary venous admixture (Qva/Qt) is based on differences in oxygen content. Significant changes in the degree of Qva/Qt, reflected by hemoglobin (Hgb) desaturation, may be masked by small changes in oxygen tension (PO2) in the vertical portion of the oxyhemoglobin dissociation curve. With the availability of oximetry it is possible to calculate Qva/Qt, on a continuous basis, from Hgb saturations. The purpose of this study was to test the validity of Qva/Qt calculated from dual oximetry by a computerized program, comparing it to bench and conventional blood gas analysis. We studied five pigs over a wide range of Qva/Qt induced by the infusion of oleic acid.

Methods. After approval of the Animal Investigative Committee of our institution, five Yorkshire swine were anesthetized with I/V droperidol and fentanyl and ventilated to normocapnia. A gas exchange analyzer (Utah Medical, MGM II) measured the FiO2 and calculated the respiratory quotient (RQ). The carotid and pulmonary arteries were catheterized with fiberoptic Swan-Ganz catheters (Oximetrix, Mountain View, CA) for continous SaO2 and $S\bar{v}O2$, and for sampling for Hgb, Hgb saturations (IL 282 Co-oximeter), pH and partial pressures of dissolved gases (IL 813 Blood gas analyzer). After stable baselines 0.1 ml/kg oleic acid was infused and blood samples taken periodically for four hours. FiO2 was titrated (range .21-.55) to prevent arterial hypoxemia. The co-oximeter was used to calibrate and validate the fiberoptic saturations in porcine blood, the catheter value being changed to match the co-oximeter for a difference of $\geqslant$ 4%. Equations used were:

$Qva/Qt=CcO2-CaO2/CcO2-CvO2$

$CcO2=(Hb*1.35)+(PAO2*0.003)$

$PAO2=FiO2(PB-PH2O)-PaCO2/RQ$

$CaO2=(Hb*1.35*SaO2)+(PaO2*0.003)$

$C\bar{v}O2=(Hb*1.35*S\bar{v}O2)+(P\bar{v}O2*0.003)$

$PO2=1/(((.015/SO2)-0.00015)^{0.370370370})$

Arterial and mixed venous oxygen contents were calculated by four different methods 1) Measured saturations from the catheters and tension derived from the saturation (VA1). 2) Measured saturations from the catheter and measured tension from blood gas analysis (VA2). 3) Measured tensions from the blood gas analyzer and saturations derived from the tensions, after pH correction[1] (VA3) 4) Measured saturation from the co-oximeter and tension derived from the saturation (VA4). Except for the manual input of Hgb, all data for the continuous computerized Qva/Qt was fed directly into a personal computer and Qva/Qt calculated and recorded every 20 sec. The results were analyzed by least square regression.

Results. 41 sets of results were analyzed and the regression coefficent, slope and intercept are shown in Table 1. The fibreoptic catheters functioned well although they often required recalibration after the infusion of the viscous oleic acid solution.

Discussion. The continuous computerized method has a significant correlation with all the other methods of calculating Qva/Qt. The correlation between VA1 and VA2 is expected as dissolved oxygen contributes minimally to the oxygen content. In fact, there would be little difference if RQ is also assumed (0.8) while calculating PAO2[2], obviating the need for a gas exchange analyzer. Despite the highly significant correlation between VA1 and VA3, there is a negative intercept of 0.08. VA3 is higher than VA1 (Fig 1) at low values of Qva/Qt and the opposite is the case with high Qva/Qt. This might be explained by the fact that the porcine oxyhemoglobin curve is to the right of the human curve (P50=32mm Hg)[3] and consequently calculating saturation from tension by an equation based on human blood would be erroneous to this effect. In conclusion, dual oximetry is an accurate and more appropriate way to calculate Qva/Qt as long as the SaO2 is < 100%. By the method described it can be calculated continously, with direct input of data into a personal computer. This may enable earlier detection of changes in pulmonary function at clinically indicated levels of FiO2, allowing better titration of therapeutic maneuvers in any critical care situation characterized by arterial hypoxemia.

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Comparison	r	Slope	Intercept
VA1 vs. VA2	0.89	0.73	0.03
VA2 vs. VA3	0.86	0.96	0.00
VA1 vs. VA3	0.98	1.31	-0.08
VA1 vs. VA4	0.99	0.98	0.00

Table 1

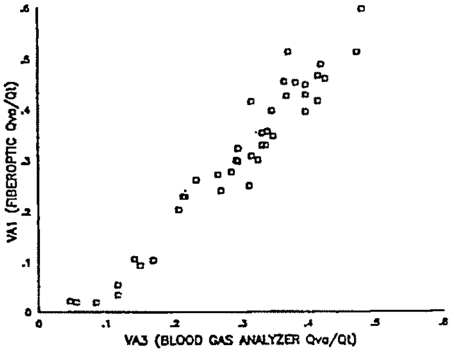

Fig. 1: X-Y plot of data distribution

Title: EFFECT OF HALOTHANE AND ENFLURANE METABOLITES ON PSEUDOCHOLINESTERASE AND ACETYLCHOLINESTERASE ACTIVITIES

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Introduction: Bromide and fluoride ions are two of the many metabolites that can be measured in the blood following the administration of enflurane and halothane anesthesia. Patients who receive enflurane and halothane anesthesia sometimes receive a second general anesthetic within a short duration for a variety of indications including bleeding, thrombus formation etc. Also, during recovery phase quite frequently the blood samples are drawn for pseudocholinesterase assay to determine the cause of apnea. Succinylcholine is also administered for short time relaxation at the end of surgery and for reintubation in the recovery room. It may be of value for anesthesiologists to know the effects of bromide and fluoride on pseudocholinesterase (PCHE) and acetylcholinesterase (ACHE) activities.

Methods: With the approval of the Institutional Review Board, we collected 10 ml of heparinized venous blood from 7 different ASA physical status I and II patients. Plasma was separated from the red cells and both plasma and red cells were stored in a refrigerator and used for cholinesterases assays.

Determination of PCHE: A kinetic method described by Kalow et al was used in the determination of PCHE and dibucaine number (DN) and fluoride number (FN) [1]. PCHE activity was expressed as nmoles of substrate hydrolyzed per min per mgm of plasma protein after an extinction coefficient for benzoylcholine was determined. Activities in the presence of fluoride and bromide were determined in the same manner using final concentrations of sodium fluoride of 5-1000 µm and sodium bromide of 10-1000 µm, respectively. DN were also performed to determine the normal genotype using a final concentration of 10 µm dibucaine.

Determination of ACHE: A colorimetric method described by Ellman et al was used in the determination of red cell ACHE activity [2]. The effects of fluoride and bromide were also studied using final concentrations of sodium fluoride of 10-5000 µm, and sodium bromide of 10-1000 µm, respectively. ACHE activity was expressed as µmoles of acetylthiocholine hydrolyzed per min per mgm protein.

Statistics: Multifactor analysis of variance (ANOVA) and multiple range testing were used to analyze the data. A p value less than 0.05 was considered significant. In addition to multifactor analysis of variance, linear regression analysis and correlation coefficients were calculated.

Results: PCHE activity: All samples had a normal DN and a normal FN indicating a normal phenotype. Fluoride at concentrations of 5 to 1000 µm inhibited PCHE activity by 8-95% (Table 1) and bromide at concentrations of 10-1000 µm did not inhibit PCHE activity.

ACHE activity: Fluoride at concentrations of 10-5000 µm inhibited ACHE activity by 1.42-69% and bromide at concentrations of 10-1000 µm did not inhibit ACHE activity.

Plots of % inhibition of PCHE and ACHE activities against log molar concentration of fluoride and bromide were shown in the Figure. The mean molar concentrations of fluoride required to inhibit 50% of PCHE and ACHE were 42 µm and 3000 µm, respectively (r= 0.95 for PCHE; r= 0.9 for ACHE).

Discussion: Inorganic fluoride is one of the metabolites of enflurane, methoxyflurane, and sevoflurane. The peak levels of fluoride in plasma occur approximately 4 hr after enflurane and sevoflurane anesthesia (around 20 µm/l) and 24 hr after methoxyflurane anesthesia (40-50 µm/l). Our data show that inorganic fluoride at concentrations of 20-50 µm/l inhibits PCHE activity by 28-56%, and ACHE activity by 1.4-2.5%.

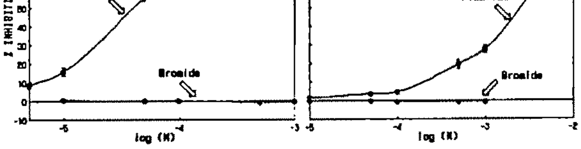
Bromide, a normal metabolite of halothane, peaks in the plasma around 24 hr following halothane anesthesia. Unlike fluoride, our data show that bromide inhibits neither PCHE activity nor ACHE activity, significantly. The clinical implications of our data are as follows: (1) in patients with suspected low or abnormal PCHE activity, the PCHE assay should be delayed at least 24 hours following enflurane anesthesia, (2) patients who undergo reoperation in the immediate recovery phase following enflurane anesthesia should be monitored closely if they receive succinylcholine, and (3) epidural ester type local anesthetics should be administered with caution in patients recovering from enflurane anesthesia.

In conclusion our present data demonstrated that fluoride at concentrations achieved with enflurane anesthesia inhibit PCHE activity significantly ($p<0.001$). Our data also show that bromide (at concentrations achieved following halothane anesthesia) has no effect on either PCHE or ACHE activity ($p>0.05$).

Table 1

Fluoride	PCHE (units) Mean±SEM	% Inhibition
Control	5.53±0.33	
5 µm	5.06±0.26	8.3
10 µm	4.62±0.20	15.8
50 µm	2.40±0.08	56.0
100 µm	1.48±0.06	73.0
500 µm	0.43±0.02	92.0
1000 µm	0.26±0.02	95.0

FIGURE



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Supported by the Study Center for Anesthesia Toxicology, Vanderbilt University.

Title: ARE INTUBATIONS BLOODY?

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INTRODUCTION. The transmission of hepatitis and HIV viruses through contact with bloody secretions and body fluids is a major concern among health care workers. Although these viruses have been isolated from human saliva, the risk of transmission from casual contact is generally considered to be negligible.[1], [2] Anesthesiologists and other medical personnel (e.g. otolaryngologists, dentists) may be at increased risk, however, because the secretions they come in contact with often contain blood. Our study was designed to investigate the incidence of blood contamination of oral and airway secretions encountered in routine anesthetic practice.

METHODS. 100 elective, general anesthetic with endotracheal intubation cases were randomly selected from 10 operating rooms in a university hospital. The anesthetics were administered by residents and CRNAs, who were unaware that their cases were to be studied. At the end of each case, all equipment that contacted the airway, including endotracheal tubes, laryngoscope blades, oral and nasal airways, suction devices and esophageal stethoscopes, was collected in a plastic container and inspected for the presence of gross blood by a person other than the individual delivering the anesthesia. Tap water was then added to the container so that all equipment was submerged for five minutes. The resulting solution was tested for the presence of occult blood with a chemstrip. The anesthesia resident or CRNA then completed a questionnaire form regarding the patient's age, route and level of difficulty of intubation, laryngoscope blade used, use of oral/nasal airways, use of suction devices and presence of coagulopathy or airway pathology. An intubation was defined as "difficult" if it required more than one attempt at laryngoscopy; it was "traumatic" if any blood was noted in the patient's mouth or pharynx during or after manipulation. All endotracheal tubes used were clear plastic, and cuffed with low pressure, high-volume balloons, if larger than 5.5 mm. Oral airways were rigid plastic dual channel airways, while nasal airways were of soft rubber. Suction devices were either rigid Yankauer-type instruments, or flexible plastic catheters.

RESULTS. (See Table 1) Of the 100 cases tested, 86 were positive for bloody secretions. 36 of those showed only occult blood, without any evidence of gross blood contamination. 14 cases were completely free from blood. 40 cases were described as "difficult" or "traumatic", and all were positive for blood, 31 (78%) gross, and 9 (22%) occult. Of the 60 non-traumatic cases, 46 (77%) were positive, 19 (32%) gross and 27 (45%) occult.

DISCUSSION. The results suggest that anesthesia personnel have considerable risk of coming in contact with bloody airway secretions during cases requiring endotracheal intubation. The number of cases positive for only occult blood indicates that observation alone is not a reliable method for assessing potentially contaminated materials. The infectivity of microscopic vs gross amounts of blood is not well established and may or may not be of concern. The large fraction of "traumatic" intubations may be explained by the liberal definition (see Methods); seemingly "normal" intubations often produced blood during suctioning or placement of airways. The present findings support the wearing of protective gloves for all anesthesia personnel performing intubation or coming in contact with airway devices.

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Table 1

	Gross Blood	Occult Blood	No Blood
All cases (N=100)	50%	36%	14%
Traumatic cases (N=40)	78%	22%	0%
Atraumatic (N=60)	32%	45%	23%

Title: PROPRANOLOL INHIBITS PLASMA PSEUDOCHOLINESTERASE

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Introduction. Beta-Adrenergic blockade is an important therapeutic tool in the management of hypertension, hypertrophic cardiomyopathy and thyrotoxicosis. Propranolol is one of the most commonly prescribed beta-adrenergic blockers so potentially it could be involved in many drug interactions. When patients receiving large doses of propranolol were given neostigmine to reverse nondepolarizing neuromuscular blockade, a profound bradycardia, which was resistant to routine atropine administration sometimes occured (1,2). In the experimental animal, propranolol prolongs and intensifies the neuromuscular blockade caused by the depolarizing agent, succinylcholine but attenuates the blockade caused by nondepolarizing agents, such as d-tubocurarine (3). The pharmacological properties of propranolol at the neuromuscular junction are therefore similar to those of a typical anticholinesterase. This conclusion prompted us to study the interaction between propranolol and cholinesterase.

Methods. The activity of plasma pseudocholinesterase (PCHE) and erythrocyte acetylcholinesterase (ACHE) were studied using Galli method (4). PCHE activity in 10 mcl sample of human serum and ACHE activity from 1 mcl of washed human red cells in 150 mcl of 0.1 M potassium phosphate buffers at pH 7.5 which was then hemolyzed by ultrasonic irradiation were studied. The enzymepreparations were added to 100 mcl of 10 mM DTNB, 1 ml of 1 mM ATCH and enough buffer to make a final volume of 3 ml. Acetylthiocholine (ATCH) was used as substrate for these enzymes. The reaction product thiocholine was then treated with 5,5 dithiobis (2-nitrobenzoic acid) (DTNB) and the amount of colored adduct formed was estimated at 412 nm using a spectrophotometer. The reaction mixture was allowed to stand for one minute before kinetic analysis to eliminate possible overestimation of activity from spontaneous hydrolysis of ATCH in stock solution.

Results. Inhibition of both PCHE and ACHE by propranolol are concentration dependent (Fig. 1). In our assay system, 0.37 mcM of propranolol inhibited 50% (I_{50}) of PCHE activity while the I_{50} of ACHE occured at 1.2 mM, a difference of more than 2 orders of magnitute. A double reciprocal plot revealed that propranolol inhibition of PCHE is noncompetive in nature. The inhibitory constant (Ki) is 5.13×10^{-7} M.

Discussion. Therapeutic plasma concentrations of propranolol for angina are estimated to be 50-100 ng/ml (5) which correspond to 0.19-0.39 mcM. For the treatment of hypertension with low renin level a much higher propranolol concentration is required. Therefore, the interaction between propranolol and PCHE is of clinic significance. Prys-Roberts demonstrated that in patients receiving large doses of propranolol the heart rate response to atropine was reduced and that to neostigmine, enhanced. This did not occur in patients on lower doses of the drug (2). We believe that his observation can be explained by PCHE inhibition at higher propranolol concentrations. In conclusion, we advise caution when administering cholinergic drugs to patients receiving high doses of propanolol.

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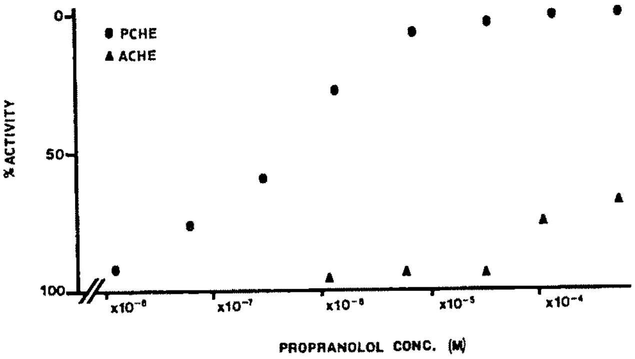

Figure 1 Inhibition of cholinesterases by propranolol

Title:

FACTORS LEADING TO HOSPITAL ADMISSION OF ELDERLY PATIENTS FOLLOWING OUTPATIENT EYE SURGERY: A MEDICARE DILEMMA.

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Introduction. There has been greater pressure to perform intraocular lens implant (IOL) as an outpatient (OP) procedure due to governmental regulation.[2,3] Recent articles have outlined the presence of several preexisting medical conditions in this group of patients.[1] There have been no reports comparing the peri-operative profile of hospital admitted patients (admission group) vs patients discharged home the same day (non-admission group) following IOL. Thus, the main purpose of our study is to compare various peri-operative factors between these two groups of patients in order to identify any significant factors that might lead to their hospitalization.

Methods. The charts of 106 patients who underwent 132 elective IOL procedures were reviewed. The preoperative medical conditions, intra- and postoperative hemodynamic changes at fixed intervals and any therapeutic interventions were all noted. After routine admission workup all patients received Neo-Synephrine 10%, Mydriacil 1%, eye drops along with premedication Demerol (25-50 mg), Vistaril (25-50 mg) by IM injection. In the O.R., monitored anesthesia care (MAC) was provided which included I.V. line, EKG, B.P. (by Dinamap) pulse oximetry, precordial stethoscope and O_2 by nasal prongs. Additional eye drops and local infiltration block was performed by the ophthalmologist with 1-2% Xylocaine with 1:200,000 epinephrine. Intravenous sedation was provided with Fentanyl (50-200 µg) and diazepan (1-10 mg) as required. Serious deviations of B.P., H.R. and persisting dysrhythmias were treated accordingly. At the end of the procedure patients were discharged to OP recovery area and then to Phase II ambulatory area.

Patients who were deemed unstable hemodynamically were evaluated by anesthesiologists and were admitted to the hospital for further stabilization and observation. These patients were grouped as admission group. The remainder of the patients, non-admission group, were sent home. The various peri-operative factors were analyzed between the two groups utilizing chi-square analysis and student's t-test. Blood pressure above 160/90 mmHg was considered hypertension and below 90/50 mmHg as hypotension.

Results. Of the total 132 procedures, 26 were performed on the other eye of the same patient, thus giving a total of 106 patients for comparison of preoperative profile. For intra- and postoperative factors, comparisons were made for 132 procedures.

A total of 19 patients (18%) were admitted to the hospital for stabilization and further evaluation. One patient was admitted both times. The remainder of patients, 87 (82%), were discharged home the same day. The various significant factors affecting the decision leading to hospital admission are given in the table. P value 0.05 or less was considered as significant. C.A.D. in the table is for coronary artery disease.

FACTORS	OVERALL INCIDENCE (n=106)	ADMISSION GROUP (n=19)	NONADMISSION GROUP (n=87)	p VALUE
PRE-OP:				
1. Age	-	78±8	72±11	0.05*
2. C.A.D.	31%	67%(12/18)	24%(21/88)	0.0004*
3. ASA Class III	48%	71%(12/17)	44%(35/80)	0.1186
4. Hypertension	45%	56%(10/18)	43%(38/88)	0.33
5. Diabetes	11%	17%(3/18)	10%(9/88)	0.43
O.R.				
6. Dysrhythmias	11%	32%(6/19)	8%(9/113)	0.0027*
7. Hypertension	71%	68%(13/19)	73%(82/113)	0.7097
Recovery Room				
8. Hypertension	14%	47%(9/19)	8%(9/113)	0.000*

Discussion. Elective OP cataract surgery with IOL implant has been one of the targeted areas of our federal legislators in their effort to cut Medicare spending as outlined in a recent report.[2] As a result a large number of these procedures are being done on the same day surgery principles. However, these elderly patients have multiple preexisting medical conditions that require in-hospital stabilization even prior to surgery as reported.[1]

The preexisting medical profile of our patients is similar to the medical profile of cataract patients reported earlier.[1] Although we could discharge 82% of our patients on the same day, 18% of our patients required hospitalization for hemodynamic stabilization and close observation. Our study seems to identify certain factors that might lead to hospitilization of these patients. Sending these patients home due to Medicare regulations would have been unsafe.

Our study indicates that near octogenarians and patients with CAD seem to require hospital admission for stabilization. The higher incidence of dysrhythmias in O.R. in admission group may reflect their poor myocardial status requiring close observation following surgery. Similarly sustained hypertension in the recovery phase is another influencing factor indicating the inability of these patients to adapt to a multitude of pharmacological interventions that occur during this procedure.

In summary, our data seems to identify certain peri-operative factors that should be considered for appropriate management of some of these elderly patients undergoing OP IOL surgery. These factors may be helpful as a guide for Medicare administrators and other third-party payers in their consideration of payment for hospitalization.

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Title: A NON-INVASIVE BLOOD PRESSURE MONITOR BASED ON ARTERIAL TONOMETRY

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Introduction. Arterial tonometry is a technique that can be used to non-invasively measure arterial blood pressure. The principles of arterial tonometry were first described by Pressman and Newgard (1), and subsequently, advanced by Drzewiecki, et al (2). Some difficulties which prevent the tonometry system from gaining clinical acceptance are its sensitivity to position, the lack of standard design and transduction technology. We currently developed a continuous, non-invasive blood pressure monitor system utilizing arterial tonometry. We evaluated accuracy, reliability and clinical acceptance of this system in patients during general anesthesia.

Methods. The non-invasive blood pressure(NBP) sensor contains the pressure transducer array, an auto mechanical positioning system, signal conditioning and multiplexing electronics, and a pneumatic bladder. A display and control unit contains more electronics, the oscillometric blood pressure module for the cuff calibration, and a CRT display for the blood pressure waveform and other signals. We used an array of 16 transducers with interelement spacing of 0.3mm. A motor drive in the transducer housing allows the operator to adjust the array position so that the array is over the artery and at least one pressure transducer is properly centered over the artery. The transducer, or active element, is identified from the pulse pressures measured by each transducer. A pneumatic system presses the transducer substrate against the skin to partially flatten the artery. The correct pneumatic, or hold-down, pressure is determined from the diastolic and pulse pressures detected by the active element.

Thirty-eight adult patients undergoing surgical procedures who require direct arterial blood pressure monitor during anesthesia and surgery at the Hokkaido University Hospital operating room. The protocol was approved by the Human Subjects Investigation Committee of the Hokkaido University , and informed consent was obtained from each patient. The invasive blood pressure (IBP) was measured on either the right or left radial artery using a Gould P23 calibrated transducer, while NBP monitor was made on the radial artery of the other side. The output of the two system signals were continuously recorded on a PCM recorder and data was used for statistical analysis.

Results. Waveforms of NBP is similar to those of IBP and changes in waveforms were quite identical as shown in Fig. 1. Regression analysis of the 4822 paired of NBP and IBP values for systolic blood pressure showed a good correlation (r=0.94, $P<0.001$) (Fig.2). there was a significant correlation between NBP and IBP values for diastolic blood pressure (r=0.86, $p<0.001$).

Discussion. We confirmed that positioning of transducers was appropriate by an automatic sensor positioning system, and that size of transducers were small enough to operate over the radial artery in adult patients. Our data indicate that during anesthesia this NBP monitor system based on arterial tonometry provide accurate, reliable and on-line blood pressure measurements in not only systolic and diastolic but continuous waveforms. It seems, although not all technical problems are solved, this NBP monitor system is potentially a useful method by which to arrive at the ;fully calibrated waveform of blood pressure on the wrist in a continuous and non-invasive fashion.

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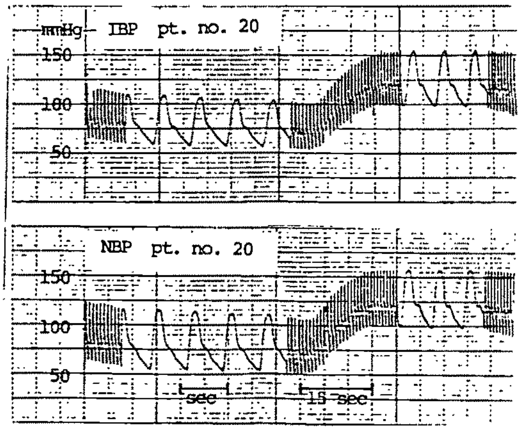

Fig.1 Comparison of invasive blood pressure (IBP) with non-invasive blood pressure (NBP)

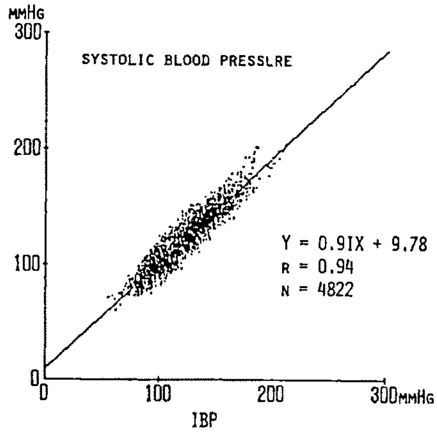

Fig.2 Correlation of NBP values with IBP values for systolic blood pressure.

Title: RECTAL METHOHEXITAL: THE EFFECTS OF CONCENTRATION AND POSITION OF THE ADMINISTRATION CATHETER

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Introduction. Rectal methohexital (M) has been used as an induction agent for children with variable success(1). When 25 mg/kg of 10% solution was used, only (84%) of the children fell asleep within 15 mins. The mean administration-sleep time was (8.3 ± 3.6 mins), and the defecation rate (15%). By diluting the M solution to 1% and positioning it in the sigmoid colon, the sleep success rate i.e. the percentage of children who fell asleep within 15 mins was (98%), the mean adminis-sleep time (6.2 ± 1.8 mins), and the defecation rate (5%) (2). In this study we evaluated the effect of M concentration (1% versus 10%), and position of the rectal catheter (sigmoid versus rectum), on the sleep success rate, the adminis-sleep time, recovery time, plasma M levels, and incidence of defecation.

Methods. Institutional approval and consent obtained from the parents of 80 children, ASA I, aged 1-5 years, scheduled for superficial operations of approximately one hour duration. The children were randomly assigned to one of four groups, (Table I).

Table I

	Dose	Con.	Catheter Position
Group I	25mg/kg	10%	sigmoid
Group II	25mg/kg	10%	rectum
Group III	25mg/kg	1%	sigmoid
Group IV	25mg/kg	1%	rectum

While the children were being comforted by their parents, M was administered either via a soft lubricated, long (5 inch) catheter which was placed in the sigmoid, or a short catheter (1.5 inch) in the rectum. The children were monitored with a pulse oximeter and continuously observed by an anesthesiologist who was unaware of M concentration, or the catheter position Sleep was defined as loss of consciousness, nonresponsiveness to verbal commands and absence of voluntary movements when unstimulated. If a child did not fall asleep within 15 minutes, the M dose was considered inadequate and the child was removed from the adminis-sleep time analysis. In the operating room, anesthesia was continued with halothane and nitrous oxide in O_2, the monitors included an apical stethoscope, automated blood pressure, EKG, pulse oximeter, temperature probe and mass spectrometry. Blood samples to measure plasma M levels were withdrawn at 15 (A), 20 (B), 30 (C), 45 (D), and 60 (E) mins from M administration, and at recovery time (F). The M plasma concentration was analyzed using reversed-phase high pressure liquid chromatography. Atropine sulphate and muscle relaxants were used to facilitate orotracheal intubation. Ventilation was mechanically controlled to keep an end tidal CO_2 of 4%. At the end of surgery, the children were extubated after regaining their protective airway reflexes. Steward's post-anesthesia recovery scoring system was used to assess recovery. Recovery time was the period between termination of all inhalation anesthetics and the time when the child was fully awake, could cough or cry and moved purposefully. Two-way analysis of variance was used to analyze the data.

Results. The sleep success rate was (95%) with 1% M solution, which was significantly ($P< 0.003$) higher than the 10% solution (70%). The sleep success rate was not affected by catheter position, it was (82.5%) for both rectal and sigmoidal groups. The adminis-sleep time was not significantly affected by M concentration nor the catheter position. Irrespective of catheter position, the mean recovery time after 1% solution was (53.2 ± 31.1 mins), which was significantly ($P< 0.0019$) longer than the 10% solution (34.4 ± 18.5 min). The mean recovery time was (44.1 ± 18.5 mins) and (43.5 ± 25.3 mins) for the sigmoid and rectal groups, respectively. The difference was not significant. The defecation rate was significantly ($P< 0.018$) higher with 1% than 10% solution. The concentration of M solutions affected significantly ($P< 0.028$) the M plasma levels at 20 mins (B) and ($P< 0.048$) at 30 mins (C). The position of the catheter did not affect significantly the plasma M levels.

Discussion. An increase in the success of induction of anesthesia with rectal methohexital was achieved by diluting the M solution to 1%. With the dilute solution, the larger volume exposes a larger surface area of the mucosa to the drug and improves absorption, and increases sleep success rate. The catheter position did not affect sleep success rate. It has been previously recommended that rectal medications should be deposited into the lower third of the rectum (3), to avoid drug absorption into the portal venous circulation and first-pass hepatic metabolism. In our study, the sleep success rate did not depend on the position of the catheter, and it was significantly affected only by M concentration. This may be due to anastomosis of the blood supply of the sigmoid and rectum. We recommend the use of 25 mg/kg of 1% solution and positioning it in the sigmoid colon.

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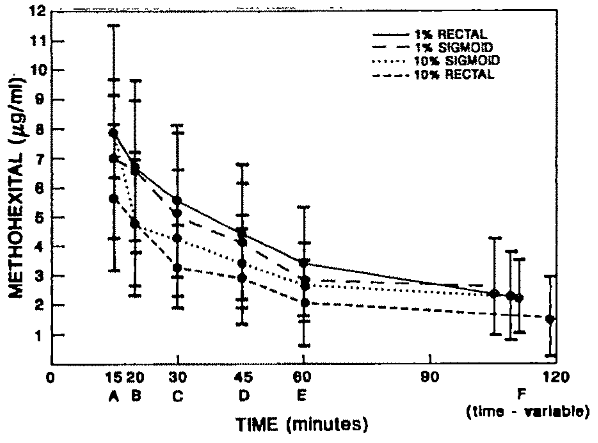
Sleep Success Rate		Admin.Sleep Time	Defeca. Rate
Conc. 1%	95%	5.7 ± 1.9 (min)	Gr. I 5%
Conc. 10%	70%	8.1 ± 11.7 (min)	Gr. II 10%
Rectal	82.5%	7.7 ± 11.0 (min)	Gr.III 20%
Sigmoidal	82.5%	6.6 ± 1.8 (min)	Gr. IV 35%

Plasma Methohexital Levels



Title: DIRECT CARDIAC EFFECT OF HYPERTONIC SALINE IN ANESTHETIZED DOGS

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Introduction. A small volume of 7.5% hypertonic saline (HNaCl) has been shown to rapidly restore systemic blood pressure and cardiac output in severely hemorrhaged animals (1-2). This cardiovascular enhancement is attributed to a vascular volume expansion and combined responses by both the peripheral circulation and the heart. Previous reports on HNaCl concentrate primarily on the systemic effects. The specific effects of HNaCl on the heart and the role of the sympathetic nervous system in mediating these effects remain unknown. The goals of this study are to examine cardiac contractility when HNaCl is administered before and after epidural and pharmacologic blockades.

Methods. Seven mongrel dogs weighing 22.6 ± 1.2 kg (S.D.) were anesthetized with 1.25% halothane in O_2 and mechanically ventilated to maintain normocarbia. Systemic arterial and venous pressures were monitored continuously. Cardiac output was measured using an aortic electromagnetic flowmeter and thermodilution via a pulmonary artery catheter. Minor axis diameter of the left ventricle (LV) was measured using sonomicrometry simultaneously with the measurement of LV pressure for the assessment of cardiac contractility. The slope (E_{es}) of the LV end-systolic pressure-diameter relationship generated during vena caval occlusion (to alter preload) was used as an index of contractility. Neural blockade was performed with xylocaine (2 mg/kg) injected at the T-4 level via an epidural catheter (7 dogs). In four dogs pharmacologic blockade in addition to epidural was achieved with propranolol (1 mg/kg), phentolamine (1 mg/kg + 0.1 mg/kg/min) and atropine (0.1 mg/kg). The efficacy of blockade was confirmed with isoproterenol, norepinephrine and acetylcholine. HNaCl (3 ml/kg) was infused intravenously over 60 seconds before and after neural blockade, with a 60 minute recovery period between each infusion. Normovolemic dogs were used to enable repeated assessment of cardiac performance after multiple doses of HNaCl and to avoid the unpredictable combined effects of neural blockade and hypovolemia. Data are expressed as mean ± S.D. Comparisons utilized the paired t-test with $p < 0.05$ considered significant. This study was approved by the institutional Animal Care Committee.

Results. Hemodynamic variables recorded during peak response to HNaCl:

	Before Blockade		After Blockade	
	Baseline	HNaCl	Baseline	HNaCl
HR (bpm)	124±21	140±13*	120±10	121±10
MAP (mmHg)	104±6	116±6*	78±17†	88±11*†
CO (L/min)	3.2±0.9	4.2±0.5*	3.0±0.9	3.5±0.8
SVR (dynes. sec/cm^5)	2707±822	2158±322*	2076±604†	1748±329†
E_{es} (mmHg/mm)	11.6±2.1	14.8±1.9*	10.6±4.6	15.2±2.0*

*p <0.05 vs baseline, †p <0.05 vs before blockade

Cardiovascular responses to HNaCl were similar whether blockade was achieved with epidural or combined epidural-pharmacologic approaches. Therefore, the data for combined blockade are not separately reported.

Discussion. Systemic vascular resistance fell by 18% following HNaCl due to a direct vasodilatory effect of hyperosmolality. HNaCl infusion exerted both positive chronotropic and inotropic effects. While neural blockade abolished the HNaCl-induced increase in heart rate, suggesting that the chronotropic effect of HNaCl was sympathetically mediated, cardiac contractility increased equally before and after neural blockade. The apparent attenuation of the cardiac output increase after neural blockade may result from a combination of beta adrenergic blockade and a decrease in venous capacitance. The results of this study demonstrate a direct effect of HNaCl on cardiac contractility; this may have an important role in restoring cardiovascular function during resuscitation.

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Title: REFINEMENTS IN THE USE OF INTRAMUSCULAR MIDAZOLAM PREMEDICATION IN PEDIATRIC DAY SURGERY PATIENTS

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Introduction. Premedicating small children for outpatient surgery is desirable but frequently impractical or unsatisfactory because it is difficult to achieve optimum timing. We evaluated the efficacy of intramuscular (IM) Midazolam, 0.1 mg/kg, given 10 minutes before parent-child separation, in preventing separation anxiety (SA) and induction crying (IC).

Methods. Following approval of our institutional Human Research Committee, informed consent was obtained from parents of 64 pediatric patients (ages 1-6 yrs ASA PS of 1 or 2) scheduled for elective day surgery. The patients were randomly divided into two groups; group A received Midazolam and group B an equal volume of normal saline, administered via a 27 gauge needle into the deltoid muscle 10 minutes prior to entering the operating room (OR). The anesthesiologist administering the agent and an independent observer were unaware of what had been administered. An additional 36 unpremedicated children whose parents had refused to participate were also assessed for SA and IC. The recorded choice of either intravenous or inhalation anesthesia induction techniques was left to the discretion of the three anesthesiologists. The independent observer was instructed to record whether the child cried at separation and/or induction. The PAR discharge time was noted. We monitored EKG, BP, and pulse oximetry. Data was analyzed using x^2 analysis, P<0.05, being chosen to represent statistical signficance.

Results. Ten minutes was an adequate time to achieve tranquilization with Midazolam and prevent SA. IC was significantly reduced with a gas induction and appeared to be reduced with an IV induction, but the sample was too small to reach statistical significance. With the exception of hiccups, in two patients, no side effects were seen. Because of different anesthetic techniques, we did not compare emergence time to PAR discharge, but no child remained in the PAR after one hour.

Discussion. It had been our clinical impression that we were not as successful premedicating with Midazolam in preventing SA and IC as had been reported (1). This was particularly so in small children. Failure appeared to be due either to inaccurate timing of drug administration or inadequate absorption (or both). Our results indicate administering Midazolam 10 mins prior to separation improved its effectiveness as a premedicant. An IM injection did not seem to cause significant additional anxiety. This plus the absence of side effects suggests that IM Midazolam still compares favorably with other recently described premedication techniques. (2,3)

MIDAZOLAM STUDY

Separation	Non-Criers	Criers	%Non-Criers	Total
Nonparticipants	15	21	41.66	36
Placebo	16	18	55.17	29
Midazolam	32*	3	91.40	35
TOTAL	63	3	63.00	100

* $p < 0.001$ ($x^2 = 20.527$; 2 d.o.f.)

Induction	Non-Criers	Criers	%Non-Criers	Total
Nonparticipants	13	23	36.11	36
Placebo	11	18	37.93	29
Midazolam	27*	8	77.14	35
TOTAL	51	49	51.00	100

* $p < 0.001$ ($x^2 = 14.248$; 2 d.o.f.)

IV vs. INHALATION INDUCTION

Inhalation Induction

	Non-Criers	Criers	%Non-Criers	Total
Nonparticipants	10	13	43.47	23
Placebo	9	10	47.36	19
Midazolam	20*	3	86.95	23
TOTAL	39	26	60.00	65

* $p < 0.01$ ($x^2 = 10.353$; 2 d.o.f.)

IV Induction

	Non-Criers	Criers	%Non-Criers	Total
Nonparticipants	3	10	23.07	13
Placebo	2	8	20.00	10
Midazolam	7	5**	58.33	12
TOTAL	12	23	34.29	35

Non-significant. $p < 0.20$ ($x^2 = 4.211$; 2 d.o.f.)

**2 patients with multiple venipunctures

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EFFECT OF LOCAL MARCAINE INFILTRATION ON POSTOPERATIVE PAIN AND MORBIDITY IN AMBULATORY SURGERY

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Introduction. Ambulatory Surgery for short selective procedures has become increasingly popular as a means of cost containment. It is, therefore, of increased importance to use surgical and anesthetic techniques that allow the patient to awaken quickly and pleasantly. These patients must be capable of going to a medically unsupervised environment with minimal side effects such as severe pain or nausea, vomiting and sedation from the need for too much narcotic analgesics and/or antiemetics. Local infiltration of the surgical site with a local anesthetic such as 0.5% marcaine has been used by many surgeons in an attempt to decrease the necessity for systemic narcotic analgesics for postoperative pain relief. Since, there have been no scientific investigations to show that this practice is of significant benefit, we undertook to study it in our breast biopsy patients.

Methods. Following approval of the Human Investigations Committee, 40 ASA Class I and II female patients scheduled for unilateral breast biopsy were asked to participate in our study. After an informed consent, each patient was given a modified Trieger test to determine preoperative baseline cognitive motor ability (1). The patients were then taken to the operating room and standard monitors were applied. Induction was with intravenous thiopental (5-7mg/kg), d-tubocurare (3mg), and lidocaine (1-2mg/kg). Anesthesia was maintained with isoflurane/N_2O/O_2 with a succinlycholine drip for relaxation. Prior to incision, based on random selection, the surgeon infiltrated the area of the incision of 20 patients with a solution of 0.5% marcaine. The other 20 patients recieved infiltration with saline. Infiltration of the solutions and postoperative assessment of the patients was done in a double blind manner.
Fifteen minutes after the patients' arrival in the recovery room, the patient was given a Trieger test and was asked to assess her pain on a linear analogue scale (2). The Trieger test and pain assessment was repeated at 45 minutes, 90 minutes and at discharge. Pain relief was provided by 10 micrograms of fentanyl intravenous or with oral Tylox. Each patient had a script for 12 Tylox to take for pain at home. Length of recovery room stay and problems such as nausea and vomiting were noted. Statistical analyses was by Student's T test for comparison between groups, chi-square tests, and Kruskel-Wallis non-parametrics tests.

Results. There was no statistically significant difference between the two groups of patients based on age, baseline Triegar drawing scores, number of cc's of solution injected or in recovery room discharge time. There was no statistically significant difference between the groups in cognitive motor function recovery as measured by the postoperative Trieger drawing scores.
There was a definite, though nonsignificant trend for more fentanyl and Tylox use and nausea and vomiting in the saline infiltrated group compared to the marcaine group in the recovery room. A statistically significant difference was found in the perception of pain as measured by the linear analogue scale between patients who received marcaine and those that received the saline infiltration. At 15, 45, and 90 minutes in the recovery room, the marcaine patients significantly rated their pain less intense (P<.05). At 24 hours, these same patients significantly rated their pain higher than their saline controls (P<.05). Concomitantly, there was a nonsignificant tendency to more Tylox use in the marcaine group in the postoperative 24 hours.

Discussion. Infiltration of the surgical site with 0.5% marcaine had no beneficial effect in decreasing the amount of anesthesia needed as measured by a more rapid return to cognitive ability or by decreasing time in the recovery room. There was a tendency to less narcotic analgesic use and nausea and vomiting in the marcaine patients in the recovery room. The statistically significant difference in pain perception between the marcaine and saline groups in the recovery room can be explained by the analgesic effect of the 0.5% marcaine at the surgical site. The situation was probably reversed at 24 hours as the marcaine effect diminished and caused a relative increase in the perception of pain in these patients. Conversely, the saline control patients experienced a gradual decrease in pain compared to the marcaine group in the postoperative 24 hours.
These results appear to question the time and expense required for marcaine infiltration of a surgical site to decrease postoperative pain perception in ambulatory surgery patients. It could be a disadvantage to these patients as their perception of pain increases after they are discharged away from the potential care and intervention of their anesthesiologist and/or surgeon.

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Title: **RANDOMIZED COMPARISON OF OUTCOME AFTER PROPOFOL OR ENFLURANE ANESTHESIA IN OPERATIONS OF LONG DURATION**

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Introduction. Interest in intravenous (*iv*) anesthesia has been revived by the introduction of propofol, the kinetics of which allow induction and maintenance of anesthesia with rapid recovery of consciousness (1). Propofol has been compared favorably to other *iv* or inhalational anesthesia methods in operations of short duration. However, it is not known how propofol anesthesia compares to other anesthetics in operations lasting more than one or two hours. To examine the properties of propofol in long operations, we conducted a randomized comparative study in patients undergoing mainly gynecological laparotomies. Safety and efficacy, as well as speed and quality of recovery were compared in patients receiving either propofol or enflurane anesthesia.

Methods. The protocol was approved by The University of Chicago Clinical Investigation Committee. Written informed consent was obtained from 60 unpremedicated ASA class I or II patients. Preoperatively, intravascular access was established with 18-gauge cannula in a vein on the dorsum of the hand or wrist. Three groups of patients were studied (propofol high, propofol low, enflurane). Prior to induction, all patients received tubocurarine 3 mg, gylcopyrrolate 0.2 mg and fentanyl 1.5 µg/kg (*iv*). Four minutes later, anesthesia was induced with either propofol 2 mg/kg or thiopental 4 mg/kg *iv* over a period of 30 seconds. Oral endotracheal intubation was performed 60 to 90 seconds after succinylcholine injection (1.5 mg/kg). Anesthesia was maintained either with propofol infusion or enflurane (0.5-2%) in nitrous oxide (N_2O) 66% and oxygen, which were started 60 seconds after intubation. The first 10 patients randomized to receive propofol (propofol high), received propofol at 200 µg/kg per minute for the first 30 minutes, 150 µg/kg per minute for the next 30 minutes and 100 µg/kg per minute thereafter. Patients 11 through 30 in the propofol group (propofol low) received 150 µg/kg per minute of propofol for the first 30 minutes and 100 µg/kg per minute thereafter. Additional analgesia was provided with fentanyl (0.05 mg boluses) and anesthesia level was adjusted with propofol boluses (0.25 mg/kg) or by adjusting the enflurane concentration to maintain hemodynamic variables within 30% of awake measurements. Other drugs administered during or after anesthesia were similar between the groups. Postoperative analgesia was provided with *iv* morphine, 5 mg at a time as needed. Early recovery from anesthesia was assessed by extubation time, responsiveness to commands, spontaneous eye opening and orientation to time and place. Emetic symptoms, nausea, retching and vomiting were evaluated every 15 minutes in the post anesthesia care unit (PACU) and at 24 and 48 hours postoperatively. Prior to surgery, immediately before discharge from the PACU, at 24 hours and 48 hours after surgery, patients were asked to complete a visual analogue questionnaire (VAQ). The following items were presented: dizziness, nausea, vomiting, difficulty sleeping, depression /sadness, tension, blurred or double vision, drowsiness, bad dreams, pleasant dreams, general feeling of weakness, hunger, headache, sore throat and ability to concentrate. Each item was followed by 100 mm long line. One end of the line was marked as "none" and the other one as "a lot". Recovery assessments were made by a research nurse who was blinded to the treatment group. Statistical analysis for continuous data was performed using analysis of variance followed by Scheffe's F-test. Chi-square test with continuity correction was used for nonparametric variables.

Results. Induction and maintenance of anesthesia was satisfactory in all of the patients. Duration of anesthesia was 149±37,152±40 and 162±44 min (mean±SD) in propofol high, propofol low and enflurane groups, respectively. Three patients in the propofol groups and one patient in the enflurane group had pain at the *iv* site during induction. There were no differences in the mean arterial pressure (MAP) or heart rate between the propofol and enflurane groups except following endotracheal intubation when MAP was significantly higher ($P \leq 0.03$) after thiopental induction. The times from discontinuation of N_2O to extubation, eye opening, response to commands, orientation and discharge from the PACU were all similar. The enflurane group had significantly more ($P \leq 0.004$) emetic symptoms in the recovery room (63% vs 23% had nausea and/or vomiting) than the propofol groups. The enflurane group experienced significantly more ($P<0.05$) dizziness, depression/sadness, difficulty to concentrate and hunger than the propofol groups in the postoperative period as assessed with visual analogue questionnaire (Table 1).

Discussion. This study demonstrates that propofol by continuous *iv* infusion is associated with fewer annoying outcome symptoms than enflurane. Analogous to other sedative-hypnotic drugs, propofol induction was associated with transient hypotension followed by hypertension and tachycardia after endotracheal intubation. However, in the propofol groups, the cardiostimulatory response was more effectively attenuated than in the enflurane group. Emetic symptoms postoperatively are distressing to the patient, and may interfere with discharge from the PACU. The enflurane group had significantly more emetic symptoms in the PACU than the propofol groups. The enflurane group experienced significantly more dizziness, depression/sadness, difficulty concentrating and hunger than the propofol groups. We conclude that propofol provided better outcome than enflurane in terms of these nonvital measures after relatively long intra-abdominal operations. While the benefits of propofol may imply that the mechanism by which it causes anesthesia or anesthetic related side-effects differs from that of enflurane, such remains to be determined.

Table 1. Visual Analogue Questionnaire (mm, Mean±SD)

	Propofol High	Propofol Low	Enflurane
Dizziness			
Baseline	0±0.0	0±0.0	1±6.6
PACU *	8±20.1	10±24.4	27±33.9
24 hours	16±30.8	6±9.5	12±20.6
48 hours	5±14.0	1±4.0	10±24.1
Nausea			
Baseline	0±0.0	2±5.9	3±13.7
PACU *	1±1.9	10±23.8	24±32.5
24 hours	4±13.3	7±21.4	12±23.6
48 hours	9±21.3	5±21.0	3±8.5
Depression/Sadness			
Baseline	28±32.1	11±23.8	21±30.1
PACU	10±31.0	0±0.0	6±18.5
24 hours *	0±0.0	2±5.3	8±16.8
48 hours *	0±0.0	1±4.2	8±16.8

* $P<0.05$ Propofol(high and low) *vs* Enflurane

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Title: RECOVERY AND PSYCHOMOTOR EFFECTS AFTER BRIEF ANESTHESIA WITH PROPOFOL AND THIOPENTAL

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Introduction. Propofol, a new intravenous anesthetic with a short distribution and elimination half life, may be suitable for outpatient anesthesia. This study was designed to compare recovery, and psychomotor skills after intravenous anesthesia with propofol and thiopental.

Methods. Twelve healthy male volunteers (22 ± 4.2 yr, 72 ± 12 kg, 176 ± 8.8 cm) participated in a double-blind, randomized, placebo-controlled, cross-over trial. The study was approved by our institutional clinical investigation committee and written consent was obtained from each subject. The subjects were studied three times with one week wash-out period between experiments. Each test day the subjects randomly received intravenously either placebo (Intralipid), propofol (2.5 mg/kg and 1.0 mg/kg 3 min later) or thiopental (5 mg/kg and 2.0 mg/kg 3 min later). Time from the beginning of the first injection until the subjects responded to command was recorded. Sitting up without help for 10 sec was attempted every 5 min after the subject regained consciousness. The ability to stand was assessed by the Rhomberg test which was attempted every 5 min starting 10 min after the subject was able to maintain a sitting position without help. Before and 1, 3, 5 and 7 hours after drug injection, residual central nervous system effects of the drugs were assessed by measuring the change in center point of gravity for 30 sec while standing with eyes closed on a computerized force-platform (body sway); and by scoring the number of correct responses on the Digit Symbol Substitution Test (DSST) for 2 min. An additional DSST was also administered at 30 min after drug injection. Paired t-test or repeated measures analysis of variance followed by Fisher PLSD test were used to compare the effects of the different treatments.

Results. Subjects responded to command and were able to sit up and stand significantly faster after propofol than after thiopental anesthesia (Table 1). No differences were noted in baseline performance in either body sway or DSST (Figures 1 and 2). Both 1 and 3 hours after administration of thiopental, body sway was greater than after propofol or placebo ($p<0.05$); no difference was seen between propofol and placebo. Both drugs impaired performance in DSST significantly at the 30 min test. The effect of thiopental was more pronounced and the difference between thiopental and propofol was significant even 5 hours after drug administration.

Discussion. The methods used to assess the residual effects of these anesthetics have previously been shown to be sensitive to the effects of other anesthetics.[1] The doses of propofol and thiopental used are similar to those used for induction of anesthesia including a top up dose if the initial dose is not adequate. Propofol anesthesia was associated with more rapid recovery and had less residual effects than a comparable thiopental anesthetic. This lack of residual anesthetic effects after propofol anesthesia may be beneficial in ambulatory surgery as earlier home readiness and street fitness could be achieved.

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Table 1. Mean ± S.D. times (min) to respond to command, sit and stand after the injection of propofol and thiopental. (* = $p<0.05$, propofol vs. thiopental, paired t-test)

	Propofol	Thiopental
Response to command	13.9 ± 2.6	18.0 ± 6.2 *
Able to sit	17.0 ± 3.3	20.4 ± 5.8 *
Able to stand	33.0 ± 6.9	62.0 ± 29.0 *

Figure 1. Mean body-sway when standing on a force platform before and 1, 3, 5 and 7 hours after drug injection.

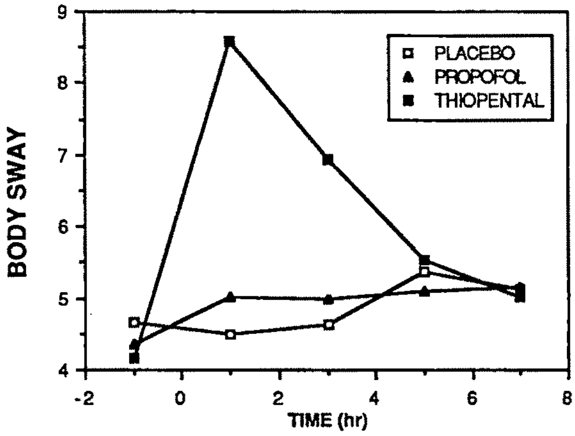
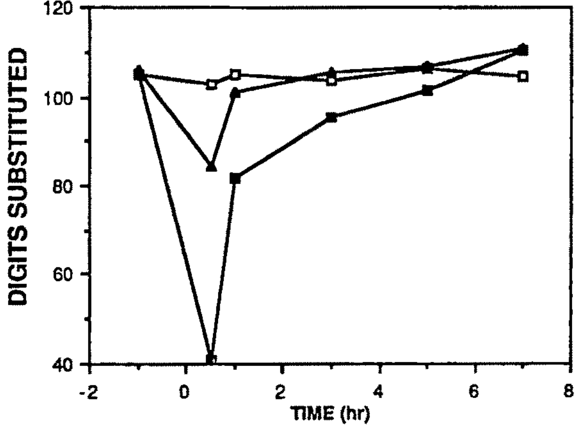


Figure 2. Mean number of digits substituted in Digit Symbol Substitution Test before and 1/2, 1, 3, 5 and 7 hours after drug injection. (For symbol definition, see figure 1)



Title: DOES ADDITION OF N_2O TO ISOFLURANE INCREASE MYOCARDIAL ISCHEMIA IN CAROTID ARTERY SURGERY PATIENTS?

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Introduction. Some recent studies implicate nitrous oxide (N_2O) as a cause of myocardial ischemia. Philbin[1] showed that N_2O increased post-systolic shortening in dogs with an imposed critical coronary artery stenosis. Reiz[2] reported metabolic and ECG evidence of myocardial ischemia with the administration of N_2O in humans. In contrast, other investigations have not documented an adverse effect.[4,5] We undertook this study to determine whether the use of 60% N_2O with isoflurane (ISO) and fentanyl (FEN) increased the incidence of myocardial ischemia and infarction above that associated with ISO and FEN alone in high-risk patients.

Methods. 61 patients scheduled for carotid artery surgery gave informed consent for this institutionally approved study. Patients were prospectively randomized to receive 60% N_2O with O_2 (N_2O/O_2) or to receive only oxygen (O_2) as the background gas. All patients received their usual cardiac and antihypertensive medications preoperatively. Thiopental (2-5 mg/kg), FEN (2-5 μcg/kg), ISO and either N_2O/O_2 or O_2 were used for induction and maintenance of anesthesia. Four patients who were studied twice were randomly assigned an anesthetic regimen for their first procedure and were given the other regimen for their second procedure. Measurements included 12 lead ECG, transesophageal echocardiography (TEE), blood pressure, heart rate and end-tidal ISO concentration by mass spectrometry. Measurements were made preinduction (except for TEE), postintubation, post carotid clamping and unclamping, during skin closure and whenever blood pressure or heart rate changed 30% from baseline ward value for at least three minutes (a hemodynamic event). TEE data were analysed by two observers for new segmental wall motion abnormalities indicating ischemia as described by Smith.[3] The 12 lead ECGs were read for baseline ST segment changes 80 msec after the J point of 1 mm or greater. In the most recent 26 patients creatine phosphokinase (CPK) and isoenzymes were obtained preoperatively and on postoperative days 1 and 2. CPK MB bands >4% of total or new ECG Q waves identified postoperative myocardial infarction. Data were interpreted by blinded observers. T-tests and chi-square analyses were used to compare groups.

Results. The two anesthetic groups of patients were comparable in ASA status, age, severity of cardiac disease and medications. Hemodynamic events did not differ in number or character between groups. Mean end-tidal ISO (± SD) was 0.55 ± 0.230 % in the N_2O/O_2 group vs. 0.815 ± 0.277 % in the O_2 group*. Fentanyl doses (μcg) were similar in each group (N_2O 154 ± - 161 vs. O_2 140 ± - 101)†. The TEE detected ischemia in 17 of 58 patients. In the N_2O group, 6 of 27 patients had at least one ischemic episode while in the O_2 group 11 of 31 patients had an ischemic episode.† TEE data were unreadable or unavailable in 8 of 66 studies. Intraoperative ECGs showed ischemic changes in 2/27 patients given N_2O/O_2 and 5/30 patients given O_2. CPKs were positive in 4 of 26 patients postoperatively. Three of these patients received O_2 only, one received N_2O.

Discussion. All indices of ischemia and infarction were more frequently observed in patients anesthetized with ISO/O_2; though the trends were consistent, statistically significant differences between the anesthetic groups were not demonstrated. We found no evidence that the addition of N_2O to ISO increased the incidence of myocardial ischemia in patients undergoing carotid artery surgery. Our results and those of others[4,5] suggest that N_2O is safe to use in patients at risk for myocardial ischemia and infarction.

Table. Myocardial Ischemia and Infarction by Anesthetic

	N_2O (%)	O_2 (%)
TEE Ischemia	6/27 (22.2%)	11/31 (35.5%)†
ECG Ischemia	2/27 (7.4%)	5/30 (16%)†
Myocardial Infarction	1/12 (8.3%)	3/14 (21.4%)†

*$p < 0.05$
†no statistical difference

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Title: Ca^{2+} INFLUX, BUT NOT INTRACELLULAR Ca^{2+} RELEASE, IS REDUCED BY VOLATILE ANESTHETICS IN A NEURAL CELL LINE

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Introduction. Recently, we could demonstrate a dose-dependent depression by volatile anesthetics (VA) of depolarization-induced Ca^{2+} influx through voltage-sensitive Ca^{2+} channels in the clonal rat pheochromocytoma cell line PC 12 (1), which possesses many properties in common with sympathetic neurons and adrenal medulla cells. PC 12 cells - expressing both nicotinic and muscarinic receptors - respond to muscarinic stimulation by mobilizing Ca^{2+} from intracellular stores and secreting catecholamines in a Ca^{2+} channel-independent manner. As shown in a recent study, ethanol is able to block this muscarine-induced cytoplasmic Ca^{2+} ($[Ca^{2+}]_i$) rise and secretion (2). However, nothing is known about the effects of VA on this second messenger-induced intracellular Ca^{2+} release in neural cells. Therefore, we investigated the effects of VA on high K^+ and receptor-induced $[Ca^{2+}]_i$ rise and catecholamine secretion in this cell line, taking advantage of the availability of an additional PC 12 variant defective in nicotinic response, which showed an entirely muscarinic-receptor-mediated reactivity.

Methods. Cells were cultured as monolayers in poly-L-ornithine-coated tissue culture flasks (37°C; 6% CO_2). The fluorescent Ca^{2+} indicator fura-2 was used to investigate the effects of halothane, enflurane and isoflurane on stimulated $[Ca^{2+}]_i$ rise, as previously described (1). Briefly, $[Ca^{2+}]_i$ was measured in suspensions of intact fura-2-loaded cells by the ratio technique at two quickly alternating excitation wavelengths (340/385nm) using a spectrophotofluorometer equipped with magnetic stirring and thermostated cuvette holder. Stimulation was carried out by addition of nicotine (100 µM), muscarine (400µM), carbachol (400 µM) or excess K^+ (56 mM). Basal and evoked secretion (dopamine, norepinephrine) were determined from monolayer supernatants by high-performance liquid chromatography (glass column 100 x 3,0 mm, packed with Nucleosil 5 C 18; electrochemical detection) using an isocratic system. $[Ca^{2+}]_i$ rise and catecholamine secretion were measured in the presence and absence of VA (1-5% v/v). Media were equilibrated with VA by bubbling (20 min, 32°C). Equilibration kinetics and concentrations were examined with a gas chromatograph.

Results. In PC 12 cells high K^+ and nicotinic-receptor-induced $[Ca^{2+}]_i$ rise and catecholamine secretion proved to be totally dependent on the presence of external Ca^{2+}. Both processes were reversibly inhibited by VA in a dose-dependent manner, showing half-maximal inhibition (IC_{50}) between 1 and 2 MAC; almost complete depression was found beyond 5% vaporized VA. In contrast, the muscarinic-receptor-mediated $[Ca^{2+}]_i$ rise (Fig.) and neurosecretion did not decrease in the presence of VA (up to 5% v/v in air). This was true for the exclusively muscarinic-receptor-mediated response of the PC 12 variant as well as for the minor muscarinic component associated with the predominantly nicotinic cholinergic response in the original cell line.

Discussion. In dog adrenal medulla, halothane selectively blocked the nicotinic, but not the muscarinic-receptor-mediated secretory response: the underlying subcellular mechanisms, however, remained unclear (3). Recently, the inhibition of the nicotinic-receptor-mediated $^{45}Ca^{2+}$ influx could be demonstrated using primary cultures of bovine adrenal medulla cells (4). In bovine medulla cells, however, stimulation of muscarinic receptors **does not** cause uptake of Ca^{2+} or release of catecholamine; thus, the potential effects of halothane on muscarinic-receptor-mediated processes could not be re-investigated using this system for technical reasons (lack of secretory response to muscarine in bovine medulla; $^{45}Ca^{2+}$ uptake). The data reported here reveal for the first time direct evidence that - in a neural cell line - VA exclusively depress channel-mediated Ca^{2+} influx and dependent neurosecretion, whereas the inositol trisphosphate-mediated intracellular Ca^{2+} release and subsequent secretion remain unimpaired. In this respect, VA differ from ethanol, which has been reported to inhibit both muscarine-stimulated $[Ca^{2+}]_i$ rise and secretion in PC 12 cells (2).

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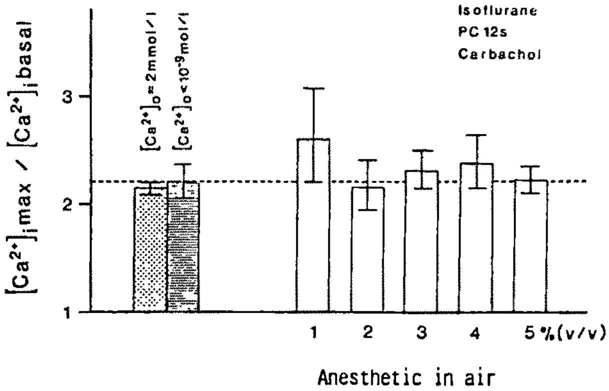

Fig. Effect of isoflurane on maximal cytoplasmic Ca^{2+} rise (expressed as a multiple of basal Ca^{2+} level). Hatched bars indicate control rise in Ca^{2+}-containing and Ca^{2+}-free medium. Geometric means ± SEM; n=5.

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Title: LIDOCAINE SLOWS THE RECOVERY OF RESIDUAL NEUROMUSCULAR BLOCK INDUCED BY ATRACURIUM AND VECURONIUM IN CATS

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Introduction. Lidocaine administered intravenously has been shown to potentiate the neuromuscular block produced by succinylcholine, d-tubocurarine and pancuronium.[1,2,3] Nowadays, atracurium and vecuronium, the non-depolarizing muscle relaxant with intermediate duration of action, are commonly used in clinical practice. To smooth the emergence of anesthesia, lidocaine is often administered intravenously at the end of surgery when patient may still have partial neuromuscular block. The purpose of our study is to quantify the interactions of lidocaine with atracurium and vecuronium.

Methods. After institutional approval, twelve cats, weighing 3.5 to 5 Kg, were divided into two groups. Group A (n=6) received atracurium and Group B (n=6) received vecuronium. Anesthesia was induced with Halothane 1-2% in air and maintained with 50% N_2O in oxygen and 0.25-0.5% halothane. Trachea was intubated without muscle relaxant and ventilation was controlled to maintain $ETCO_2$ at 30-35 mm Hg. Electrocardiogram was monitored and esophageal temperature was maintained between 35-37°C with surface warming. Blood pressure was monitored non-invasively from the tail artery. The peroneal nerve was stimulated with rectangular supramaximal pulse of 0.2 ms duration in train-of-four (TOF) mode (2 Hz) once every 20 seconds. Twitch response of the tibialis anterior muscle was recorded electromyographically. After stabilization of the twitch response, atracurium 100-150 ug/kg (Group A) or vecuronium 15-40 ug/kg (Group B) was administered intravenously to induce 95% of twitch depression. Neuromuscular block and recovery were recorded. Thirty minutes after complete recovery of train-of-four, atracurium or vecuronium in the same dose was given intravenously. When the 1st twitch of TOF had returned to 50% of control, lidocaine 2 mg/kg was administered intravenously at a different IV line. Effect of lidocaine on the progress of spontaneous recovery was quantified. To rule out the possibility of "recurarization", lidocaine 2 mg/kg was given intravenously again 20 minutes after complete recovery of the train-of-four. Results are presented as the Mean ± SEM. The Student's t-test was used to compare the results. Statistical significance was defined as $P < 0.05$.

Results. Effect of lidocaine on the recovery of atracurium is shown on the Figure. Table 1 shows that lidocaine deepened the residual block. Table 2 shows that lidocaine delayed the progress of residual block. No effect on twitch was observed in any cat when lidocaine was given after TOF had completely recovered for 20 min.

Discussion. Injection of 2 mg/kg of lidocaine during a partial neuromuscular block established by atracurium and vecuronium produced a depression of the residual block. It prolonged to 1.3 - 1.4 x of control, the time taken for neuromuscular recovery to progress from the point of $T1 = 50\%$ of TOF ratio = 0.75. Carpenter et al showed that the addition of lidocaine during pancuronium infusion increased twitch depression by 20% in the cat.[2] In another study a 25% augmentation of d-tubocurarine twitch depression was observed when 5 mg/kg of lidocaine was given intravenously in cats.[1] In our study the dose of lidocaine was closer to clinical dosage. Clinically residual curarization had been observed in the recovery room in 33% of patients received pancuronium and 6.6% of patients received atracurium.[4] Addition of lidocaine may aggravate the problem in occasional sensitive patients.

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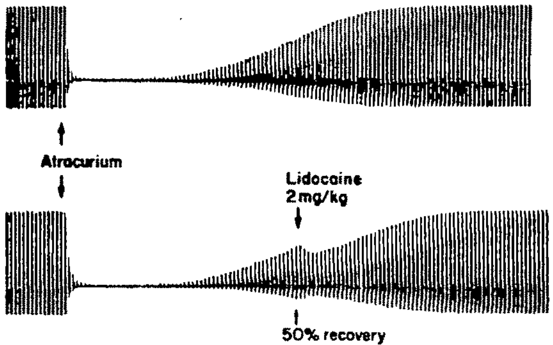
Table 1.

	% block before lidocaine	% block 1 min. after lidocaine	P
Atracurium	51 ± 1.5	57 ± 1.2	<0.005
Vecuronium	51 ± 2.1	55 ± 1.3	<0.025

Table 2.

	Time (min.) from $T_1 = 50\%$ to TOF ratio = 0.75		
	without lidocaine	with lidocaine	P
Atracurium	9.9 ± 0.9	14.4 ± 0.8	<0.005
Vecuronium	10 ± 1.6	13 ± 1.7	<0.005



Figure

Influence of cardiac output on estimated hepatic blood flow during isoflurane-induced hypotension

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Introduction: Isoflurane is an effective hypotensive agent that maintains adequate blood flow to the vital organs. The liver, however, has limited ability to autoregulate and during sodium nitroprusside-induced hypotension, cardiac output appears to be the determining factor of liver blood flow [1]. This study is accordingly designed to investigate the influence of cardiac output on estimated hepatic blood flow (EHBF) using indocyanine green (ICG) clearance during isoflurane-induced hypotension.

Method: The study was approved by the Human Ethics Committee and consents were obtained from six patients, age 23 - 63, presenting for cerebral aneurysm clipping. All were free from cardiac or liver disease. Anesthesia was induced with thiopental 5 mg./kg., succinylcholine 1 mg./kg., and lidocaine 1.5 mg./kg., and maintained with isoflurane, oxygen and pancuronium. Hypotension was induced by increasing the inspired isoflurane concentration to obtain the desired level of blood pressure. Cardiac output by thermodilution was determined during normotension, steady hypotension as well as post-hypotension. Estimated hepatic plasma flow (EHPF) was determined by injecting indocyanine green 0.5 mg./kg. into a central vein and collecting serial arterial blood samples at 0, 1, 2, 4, 6, 8, 10, and 12 minutes. The plasma concentration of ICG was measured using a spectroscopic method. The EHPF was calculated from the rate constant (K) of the logarithm of the plasma ICG concentration time curve and extrapolated zero time level Cp_0 according to the equation. $\mathrm{EHPF} = \frac{\mathrm{K \times dose}}{\mathrm{Cp_0}}$

EHBF was obtained by correcting the plasma value for the hematocrit measured at the time of ICG injection. For statistical analysis, one-way analysis of variance for repeated measures and Bonferroni's t-test as well as linear regression analysis were used. A p value of < 0.05 was considered significant.

Results: All patients were successfully studied without complications. Cardiac output did not change significantly during hypotension, with 3 patients showing a small increase and the other 3 a small decrease. There was a significant increase in cardiac output following the recovery of blood pressure although there was no rebound hypertension. Similarly EHBF did not change significantly during hypotension. (Table). A linear regression analysis demonstrated a significant correlation between EHBF and cardiac output. To demonstrate that this relationship is consistent for each individual, a linear regression analysis was performed on percentage change in cardiac output and EHBF during hypotension. A significant correlation was again demonstrated. (Figure) The leftward position of the regression line indicates that there is a 9% increase in EHBF from induction of isoflurane-induced hypotension alone, provided that the cardiac output stays unchanged. Interestingly, the influence of cardiac output on EHBF only held true for the change from normotension to hypotension. During the recovery phase, the increase in cardiac output was accompanied not by a corresponding increase in hepatic blood flow, but rather, a small decrease, suggesting that the increase in cardiac output during this phase may be mediated by sympathetic stimulation, which causes splanchnic vasoconstriction.

Discussion: Similar to previous investigation on sodium nitroprusside-induced hypotension, we demonstrated that during isoflurane-induced hypotension, the hepatic blood flow is independent of blood pressure and is primarily determined by the cardiac output. In addition, the decrease in hepatic blood flow despite an increase in cardiac output in the recovery phase suggests that sympathetic stimulation during isoflurane anesthesia may cause splanchnic vasoconstriction but this needs to be confirmed by further investigations.

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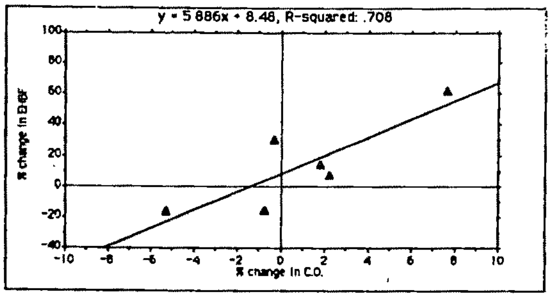
	NORMOTENSION	HYPOTENSION	RECOVERY
Insp. ISO (% ±SE)	1.0±0.1	2.04±0.1	1.0±0.1
Mean BP (mmHg±SE)	75±3	45±1*	77±5
Cardiac Output (l/min±SE)	5.19±0.5	5.22±0.47	5.76±0.63*
EHBF (ml/min ±SE)	1078.53±128.8	1161.95±87.28	1020.82±160.18

*P<0.05, significantly different from normotensive values



Title: **NITROUS OXIDE DOES NOT IMPAIR POSTOPERATIVE PULMONARY FUNCTION**

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Introduction. A previous report found that patients given nitrous oxide (N_2O) had impaired postoperative oxygenation compared to patients whose anesthetic did not include N_2O.[1] However, humidification of inspired gasses for only those patients who did not receive N_2O confounded interpretation of these results. We designed the current study to define the role of N_2O in the development of pulmonary dysfunction.

Methods. 253 patients presenting for elective total hip arthroplasty, carotid endarterectomy, or transphenoidal hypophysectomy gave informed consent to be included in this institutionally approved study. Patients were randomly assigned to receive N_2O 60%/O_2 40% (n=122) or O_2 100% (n=131). All patients received isoflurane, thiopental, and vecuronium, and a heat and moisture exchanger (Humid-vent®) was inserted at the end of the endotracheal tube following intubation. Fentanyl and edrophonium/atropine were administered at the discretion of the anesthesiologist. Controlled mechanical ventilation and five liter/minute total gas flows were continued throughout the operation.

Oxygen saturation was measured for one minute with pulse oximetry (Ohmeda Biox IV) preoperatively, at 60 and 120 minutes postoperatively, and on postoperative days 1, 2, 3 and 5. Measurements were made with the patient breathing room air, and the lowest O_2 saturation was recorded. Additionally, 129 patients having carotid or hip surgery were monitored with continuous pulse oximetry with hard copy printout of O_2 saturation (Ohmeda Biox II) during the intraoperative and immediate 24-hour postoperative period. A history of smoking habits and complaints of cough or sputum was obtained preoperatively and patients were interviewed the day after their operation for new complaints of cough or sputum production. All data collection, analyses, and patient interviews were performed by individuals unaware of the allocation to receive or not receive N_2O. T-tests, Fisher's exact probability test, and chi-square analyses were used to compare the data from the two anesthetic groups.

Results. Factors which might influence postoperative oxygenation including patient age, smoking history, length of operation, and dose of intraoperative narcotic were similar in each group (Table 1). New complaints of cough and sputum production occurred in 16% and 15% of patients given N_2O and in 22% and 17% of patients given O_2 only. The percent decline in O_2 saturation measured at 5 intervals postoperatively was slight (average decline < 2% in the PAR and < 1% by postop day 1) and did not differ between the 2 anesthetic groups (Table 2). Documented episodes of hypoxemia (O_2 saturation < 85%) were frequent in both anesthetic groups (Table 3). Hypoxemia in the operating room occurred in 5 patients given N_2O; all episodes were transient (< 2 min); 4 episodes occurred at the termination of anesthesia following extubation; one patient developed desaturation during surgery, which resolved following discontinuation of N_2O. No patients given 100% O_2 developed intraoperative hypoxemia (significantly different from patients given N_2O). However, N_2O exposure did not increase the risk of postoperative hypoxemia.

Discussion. We did not confirm the implied results from the data of Gawley and Dundee[1]: N_2O with isoflurane produced no greater postoperative pulmonary dysfunction than anesthesia with isoflurane and 100% O_2. However, some patients given N_2O (but not O_2 only) did develop transient intraoperative hypoxemia; most of these episodes occurred at the end of the anesthetic and may have been related to diffusion hypoxia and/or the smaller reserve of O_2 when N_2O was used. Irrespective of anesthetic technique - patients have a significant incidence of episodic hypoxemia during the first 24 hours following carotid endarterectomy and total hip arthroplasty.

Table 1

	N_2O	O_2
Age (yrs)	53 ± 13	54 ± 14
Smoker (%)	30/122 (25%)	28/131 (21%)
Duration Op(min)	175 ± 44	176 ± 45
Fentanyl (μgm)	224 ± 134	229 ± 112

Values are $\bar{X}$ ± SD or %

Table 2 All Surgeries, Postop Decline in (%) O_2 Sat

	1 hr	2 hr	1 day	2 days	5 days
N_2O	-1.39	-1.21	-0.83	-.88	-.84
O_2	-1.47	-1.64	-0.74	-.90	+ .133

Table 3 Patients with Hypoxemia (O_2 Sat < 85%)

	N_2O	O_2
Intraoperatively		
Carotids	2/21 (10%)	0/26 (0%)
Hips	3/41 (7%)	0/41 (0%)
Total	5/62 (8%)*	0/67 (0%)
Postoperatively		
Carotids	5/28 (18%)	4/33 (12%)
Hips	19/45 (42%)	15/47 (32%)
Transph	0/49 (0%)	1/51 (2%)
Total	24/122 (20%)	20/131 (15%)

*p < 0.05, 2-tailed Fisher's exact test.

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TITLE: PHARMACOKINETICS OF LABETALOL IN POST-CAROTID ENDARTERECTOMIZED PATIENTS

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INTRODUCTION: Labetalol is a unique antihypertensive agent possessing nonselective beta as well as selective alpha$_1$ receptor blocking properties being used for the treatment of hypertensive emergencies, chronic hypertension and hypertension following various surgical procedures. Hypertension after carotid endarterectomy is common with an incidence as high as 56%. We have previously shown that labetalol is effective in the treatment of post-carctid endarterectomy hypertension[1]. The purpose of the present study was to evaluate the pharmacokinetics of labetalol after intravenous administration in the treatment of post-carotid endarterectomy hypertension.

METHODS: 18 ASA II-IV patients (mean age of 64 years, mean weight 71.7 kg) undergoing elective carotid endarterectomy gave their informed consent to participate in this IRB approved study. Anesthetic management was standardized among all patients.[1] Once entrance blood pressure criteria was reached, labetalol was administered as a 20 mg dose over 2 minutes, followed by a 40 mg bolus dose every 10 minutes until blood pressure was reduced to a predetermined level. Venous blood samples were drawn from each patient immediately before administration of labetalol, at 5, 10 and 30 minutes after each labetalol dose at 1,2,3,4,6,8,12 and 24 hours after the last dose of labetalol. Plasma labetalol concentration was measured by HPLC utilizing the method of Hidalgo and Muir[2] with some modifications. Using 1 ml of plasma, the lower sensitivity of this assay in our laboratory is 5 ng/ml with a coefficient of variation of less than 7% and 0.4% at plasma labetalol concentrations of 5 ng/ml and 400 ng/ml, respectively. Concentrations of labetalol higher than 400 ng/ml were reanalyzed using 0.5 ml of plasma. There is no interference with this assay by any of the drugs patients received during their course of anesthesia.

PCNONLIN was used to characterize the exponential terms of the decline in the plasma concentration - time course of labetalol. Lagrange technique was then used to calculate the total area under the plasma concentration-time curve (AUC). The systemic plasma clearance (Clp) of labetalol was measured as the ratio of the dose/AUC. The apparent steady-state volume of distribution (Vdss) was measured as the ratio of (dose)(AUTC)/(AUC)^2 where AUTC is the first moment of the labetalol plasma concentration-time curve. Data is presented as mean (±SD).

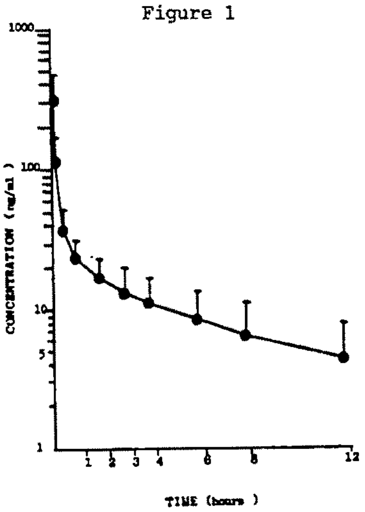
RESULTS: 11 of the patients required a 20 mg dose, 3 patients required a total of 60 mg and 4 required a total of 100 mg of labetalol. Figure 1 displays the plasma concentration-time profile in the 11 patients who received a single 20 mg dose of labetalol. The concentration - time data was best described by a two compartment model. The plasma concentration of labetalol decreased rapidly after IV administration with a distribution half-life (T1/2 alpha) of 5(3.4) minutes, followed by a slower elimination phase [T1/2 beta = 6.43(4.08) hrs]. In most patients receiving a 20 mg bolus dose the plasma concentration of labetalol was undetectable at the 24 hour sampling. The pharmacokinetic parameters did not appear to be changed in patients who received higher doses. The calculated pharmacokinetic parameters of labetalol in the 18 patients are summarized in table 1.

CONCLUSIONS: Labetalol is a relatively rapid acting antihypertensive agent. In our study the plasma concentration-time of labetalol behaved according to a two compartment model. The pharmacokinetic values obtained in this study are similar to those reported in other clinical settings. As in previous investigations, we also observed a wide variability in the pharmacokinetic parameters among the patients. While labetalol has a short distribution and a relatively short elimination half-life its antihypertensive effect lasts significantly longer. The discrepancy in concentration-response might be that labetalol binds to the adrenergic receptors for a long period of time. However, further clarification is indicated.

Table 1:

T1/2 Alpha	5.0 (3.4) min.
T 1/2 Beta	6.43 (4.08) hrs.
AUC	512.4 (399.5)
Clp	1563.6 (516.4) ml/min.
Vdss	8.17 (3.82) l/kg

Figure 1



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TITLE: ALFENTANYL VS. ISOFLURANE IN OUTPATIENT LAPAROSCOPY: AN EVALUATION OF MORBIDITY AND COST

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INTRODUCTION: Intraoperative hemodynamic stability, postoperative morbidity and cost must all be considered when evaluating anesthetic agents for outpatients. We conducted this prospective study to compare alfentanyl (ALF) and isoflurane (ISO) for outpatient diagnostic laparoscopy (LAP).

METHODS: After receiving approval from the Human Studies Committee, we studied 38 ASA PS I and II women undergoing LAP in our Day Surgery Unit (DSU). We recorded patient age, ASA physical status (PS), body mass index (BMI), blood pressure and temperature. Patients were then randomly assigned to receive ALF or ISO. At minute (min) 0, each patient received 0.01mg/kg atropine IV. At min 1, all patients began breathing 100% O_2. Thiopental, 6mg/kg and succinylcholine, 1.5mg/kg were given IV at min 1.75. At min 2, 70% nitrous oxide (3L O_2, 7L N_2O) was begun and patients received either 3% ISO or 25mcg/kg ALF. Laryngoscopy and intubation were performed at min 4. At min 6, an ALF infusion (0.5mcg/kg/min) was begun in ALF patients. ISO was continued in ISO patients. A succinylcholine infusion was used to provide muscle relaxation in both groups. Mean arterial pressure (MAP) and heart rate (HR) were recorded at one min intervals for the first seven minutes. If intraoperative hypertension occurred or awareness was suspected in ALF patients, a 25mcg/kg bolus of ALF was given, or the infusion rate was increased to a maximum of 1.5mcg/kg/min. ISO was then administered if the additional narcotic did not control these responses. In ISO patients, the concentration of ISO was adjusted at the discretion of the clinical anesthesiologist and monitored using a mass spectrometer. (The anesthesiologist was not permitted to see mass spectrometer ISO readings). O_2 and N_2O flows were reduced to 1L O_2 and 2.3L N_2O in all groups when adequate depth of anesthesia was achieved. End tidal CO_2 was maintained between 35 and 40 torr throughout the study. We recorded total dose of ALF and calculated the total amount of ISO administered using the average inspired concentration and carrier gas flows. Recovery room (RR) nurses were unaware of patient groups. RR admission and discharge temperature, RR morbidities, duration of RR stay and post-discharge morbidities were recorded. We calculated hospital purchase costs for the total amounts of ALF and ISO administered per patient. Chi-square analyses and t-tests were used to determine the significance of differences between ALF and ISO groups.

RESULTS: ALF and ISO groups were similar with regard to age, BMI, blood pressure, pre- and postoperative temperature, duration of anesthesia and surgery, total dose of succinylcholine and complaints of pain. MAP and HR were significantly greater in the ISO group 1 min after laryngoscopy and intubation (34 torr, 32 BPM) than in the ALF group ($p<.05$). Twenty percent of ALF patients required ISO to control intraoperative awareness or hypertension. ALF patients had a higher incidence of nausea and vomiting in the RR and following discharge than ISO patients (Table). Complaints of pain were comparable. Hospital purchase costs for the principal anesthetic agents (ALF or ISO) were approximately sevenfold greater for patients receiving ALF (Table).

DISCUSSION: ALF effectively attenuated the hemodynamic response to intubation while ISO did not. In a previous study of similar patients, fentanyl 3mcg/kg prior to induction also failed to attenuate this response.[1] Our attempt to provide identical, rapid time courses during induction with both ISO and ALF may not have allowed sufficient time to achieve clinically effective levels of ISO. Intraoperatively, ALF failed to provide adequate anesthesia in 20% of patients and the per patient cost of ALF was seven times higher than ISO. The higher incidence of RR and post-discharge nausea and vomiting in ALF patients reflect the observations of other authors during examination of narcotic- suppplemented anesthesia for LAP.[2]

CONCLUSION: In this comparison of two commonly used outpatient anesthetic techniques, only ALF was effective in blunting hemodynamic responses to intubation. Control of such responses may assume greater importance in less healthy groups of patients. The striking difference in cost of agents and the lower incidence of postoperative morbidities in the ISO group, however, is an important consideration in selecting an anesthetic technique for any patient population.

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TABLE:

	ISO	ALF
N	18	20
Time (hr)		
Surgery	.64	.59
RR*	1.75	2.04
Average ISO cc/liquid	2.04	---
Average ALF dose mcg/kg	---	68
Average Agent Cost ($)*	1.37	9.08
Min 5		
MAP*	130	95
HR*	127	95
RR (%)		
Nausea*	11	50
Vomiting	11	45
Pain	44	45
Post DC (%)		
Nausea	33	53
Vomiting*	11	47
Pain	77	74

*$p<.05$

Title: NEUROMUSCULAR EFFECTS OF MIVACURIUM CHLORIDE IN MAN UNDER ENFLURANE OR HALOTHANE ANESTHESIA

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Introduction. Mivacurium chloride is a new nondepolarizing neuromuscular blocking relaxant. Recent data on humans indicate that it is potent and short-acting with an estimated ED_{95} of 0.09-0.10 mg/kg and a 25-75% recovery index of 5-7 min. under narcotic anesthesia (1). This is a progress report of an independent study of its clinical neuromuscular pharmacology concerning the effects of inhalational anesthetics.

Methods. Sixty-three elective surgical patients, ASA I-II, aged 19-66, weighing 45-104 kg, gave informed consent and were studied with institutional approval. Patients with history of abnormal reactions to anesthetics, hepatic, renal or neuromuscular abnormalities, or taking antihistamines were excluded. Premedication consisted of meperidine 50-75 mg i.m. and/or diazepam 10 mg p.o. Anesthesia was induced with thiopental 4-10 mg/kg i.v. and maintained with N_2O 50-70% and enflurane 0.6-1.5% or halothane 0.4-1.0% (end-tidal). Fentanyl 0-4 μg/kg and/or midazolam 1-2 mg were supplemented as needed. Ventilation was controlled manually before intubation of the trachea and with a ventilator afterwards. $PaCO_2$ was 30-40 torr. Core temperature was 35.5-36.5°C. The systolic, mean and diastolic BP were determined automatically every minute. ECG and blood oxygen saturation were continuously monitored. All patients received 0.4-0.8 liters of D5LR during the preparation. Fifteen minutes after introduction of enflurane or halothane, when vital signs, anesthetic level and neuromuscular response were steady, first bolus dose of mivacurium chloride was injected i.v. rapidly. Following the block, neuromuscular response was allowed to recover completely. Subsequent relaxation was maintained by repeat boluses or infusion of mivacurium chloride. Following injection of the initial dose of mivacurium chloride, vital signs were observed for 5 minutes before surgical stimulation or tracheal intubation was attempted. At the end of surgery, the block was allowed to recover completely or was reversed. The ulnar nerve was stimulated at 0.1 Hz with 0.2 ms supramaximal rectangular electric pulses. Neurally evoked compound EMG of the first interosseous muscle of the hand was quantified. All data are mean ± SEMs except otherwise indicated.

Results. The onset and potency of neuromuscular block of mivacurium chloride were:

	enflurane anesth.					halothane anesth.	
Dose (mg/kg)	0.03	0.04	0.05	0.08	0.15	0.03	0.15
n	9	9	9	9	9	9	9
block (%)	19±9	44±10	45±11	70±10	98±1	10±5	96±2
full onset (min)	6.2±1.3	6.0±1.9	6.0±0.6	6.0±0.4	4.8±0.5	5.1±0.7	4.6±0.5

The ED_{25}, ED_{50}, ED_{75} and ED_{95} of mivacurium chloride under enflurane anesthesia were 0.040, 0.053, 0.070, and 0.106 mg/kg, respectively. The 25-75% recovery indices of neuromuscular transmission for the enflurane and halothane groups were 9.5 ± 2.7 and 7.3 ± 1.2 min., respectively. Comparisons of potency and recovery indices of mivacurium chloride between halothane and enflurane groups by Student's t tests revealed no statistically significant differences, $p > 0.4$ in all instances.

Cutaneous reactions were limited to mild redness over the face, neck, and shoulders occurring in 7 patients. Cardiovascular changes were benign for all dose of mivacurium chloride tested, and required no specific treatment in any patient.

Discussion. Mivacurium chloride is short-acting and nondepolarizing (2). Its cardiovascular and cutaneous side effects are mild and most likely due to histamine release (1). The potency of mivacurium chloride we recently obtained with narcotic-N_2O anesthesia under the same protocol were: ED_{25}=0.039, ED_{50}=0.045, ED_{75}= 0.063, and ED_{95}=0.088 mg/kg, respectively. Enflurane therefore appears to have no effects on the neuromuscular action of mivacurium chloride under our experimental conditions. Similarly, the potentiation by halothane at the concentration we used is negligible, if any. The recovery indices do not reach statistically significant differences when enflurane and halothane groups are compared with narcotic group. We concur that in man, mivacurium chloride is a desirable neuromuscular relaxant under clinical anesthesia (1,2). The lack of potentiation by enflurane or halothane needs to be reconciled with Brandom, et al (3) and Powers, et al (4) who observed that halothane or isoflurane anesthesia reduced the infusion requirement of mivacurium chloride, suggesting potentiation.

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Title: REVERSAL OF DOXACURIUM AND PANCURONIUM INDUCED NEUROMUSCULAR BLOCKADE

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Introduction. Doxacurium chloride (DOX) is a long-acting, nondepolarizing muscle relaxant with minimal cardiovascular side effects. We have shown in a previous study that 0.05 mg/kg DOX (2 x ED95) provides good intubating conditions in 4 to 5 minutes, and has a clinical duration of 1½ hours defined as time to 25% recovery of T1 (1). T1 is defined as the first response in a train-of-four (described below) delivered every 10 seconds and expressed as a percent of beginning baseline level. These data are similar to those of other published clinical trials (2,3). Unlike other studies, however, we systematically evaluated both T1 and T4:T1 ratio after reversal. We found that T1 achieved 90% of baseline in 10 minutes. In contrast, the T4:T1 ratio lagged, recovering to a mean of only 0.6 at 20 minutes. We wished to know if the delayed recovery of the T4:T1 ratio was a function of enflurane inhalational anesthesia and large doses of DOX or if it also occurred with equal potent doses of pancuronium. We therefore studied an additional 8 patients with a similar protocol using pancuronium (PAN) at 2 x ED95. Presented here is the new data from the PAN group along with the DOX reversal data presented previously.

Methods. This study was approved by the Human Studies Committee of the Institutional Review Board. Patients were of ASA Class I or II, free of hepatic or renal disease, and gave informed consent. Inhalational enflurane anesthesia and adductor pollicis tension monitoring were performed as previously described (1). Eight patients received DOX 0.05 mg/kg (2 x ED95) 2 minutes after induction. Eight patients received PAN 0.15 mg/kg in an equipotent dose (2 x ED95) (4). Anesthesia was maintained as previously described after successful tracheal intubation. At the end of surgery, reversal was attempted when T1 had spontaneously recovered to approximately 25% of baseline. In the DOX group either neostigmine 0.045 mg/kg, 0.06 mg/kg, or edrophonium 1 mg/kg were given in a randomized fashion. In the PAN group all patients were given neostigmine 0.045 mg/kg. No differences in reversal characteristics existed between patients given neostigmine 0.045 mg/kg, neostigmine 0.06 mg/kg, or edrophonium. Both T1 and T4:T1 ratio were recorded at reversal and 5 minute intervals for 20 minutes or until the patient was moved from the OR. Results are reported as mean ± SD. An unpaired t test was used for statistical comparisons. $p < 0.05$ was considered statistically significant.

Results.

Table 1. T1 as percent of baseline. Time = minutes after reversal. SD = standard deviation. n = number of patients.

Time	Doxacurium			Pancuronium		
(min)	T1%	SD	n	T1%	SD	n
0	26	3	7	27	4	8
5	87	14	7	79	18	8
10	92	10	7	98	8	8
15	91	17	5	99	3	8
20	92	11	8	99	3	8

Table 2. T4:T1 ratio. Time = minutes after reversal. SD = standard deviation. n = number of patients. * = $p < 0.05$ between groups.

Time	Doxacurium			Pancuronium		
(min)	T4:T1	SD	n	T4:T1	SD	n
0	0.09*	3	7	0.16	7	7
5	0.51	10	7	0.53	13	8
10	0.58*	16	7	0.75*	8	8
15	0.57*	10	5	0.81*	10	8
20	0.60*	18	8	0.83*	11	8

Discussion. Previous reports have utilized T1% of baseline alone as an indicator of blockade reversal and have found DOX to be readily reversible with standard doses of reversal agents (2,3). Similarly, these data show in both the DOX and PAN groups T1 is reversed quickly without statistically significant differences between groups. The T4:T1 ratio recovered to 0.75 at 10 minutes and 0.83 at 20 minutes in the PAN group. The DOX group achieved a mean T4:T1 ratio of 0.62 at 20 minutes.

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4. Savarese JJ et al: Anesthesiology 47:277-284, 1977

Title: LEFT VENTRICULAR PERFORMANCE DURING PROPOFOL AND METHOHEXITAL ANESTHESIA: ISOTOPIC VENTRICULOGRAPHY AND INVASIVE CARDIAC MONITORING.

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Introduction: Methohexital (M) [1,2] and propofol (P) [3] are suitable for continuous infusion anesthesia. No study compares the effects on left ventricular (LV) performance of these two agents under comparable conditions. We, therefore, determined the effects of either M or P on LV function using gated radionuclide ventriculography (RNV) and invasive cardiac monitoring, in unpremedicated patients with chronic coronary artery disease (CAD).

Methods: After institutional approval and informed consent, 22 ASA III patients (50-78 yr), undergoing major urologic surgery were randomly and equally assigned to two groups to receive either M or P. All patients had documented angina pectoris secondary to CAD. None had a history of congestive heart failure or valvular heart disease. No patients were premedicated but all received their usual medications (nifedipine and isosorbide) up to and including the morning of surgery. The study was performed in the nuclear medicine laboratory just before surgery. Heart rate (HR) was measured from lead II of the ECG. A 7.5 French thermodilution Swan Ganz catheter and a radial artery cannula were inserted under local anesthesia. All patients were studied by RNV using first-pass and ECG gated equilibrium blood-pool technique with in vivo red blood cells labeled with 99 m Technetium (Tc).[4] An in vivo preparation containing 2 mCi of 99 m Tc pertechnetate (Technetium CEA Elumat 300) was counted 10 cm away from a gamma-camera. A first-pass study was realized in the 45° left anterior oblique position following the iv injection of this source, permitting the estimation of the attenuation factor (AF). AF was assessed as the ratio Q / (C x MTT) where Q = injected counts / sec, C = integrated counts during the first transit and MTT = mean transit time of the bolus through the left ventricle during the first transit. Then a second in vivo preparation containing 20 mCi was injected. At blood activity equilibrium, the data synchronized with ECG were transferred to a computer for processing and displayed on a color monitor. End-diastolic counts, end-systolic counts and ejection fraction (EF) were calculated for 1.5 minutes apiece. By using the AF, exact numerical values in ml of end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and densitometric cardiac output (deCO) were obtained. First-pass isotopic CO and deCO were compared in each patient for validation of the method. Series of measurements including HR, mean arterial blood pressure (MAP), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), thermodilution output (thCO), EF, EDV and ESV were collected. Blood samples were withdrawn for blood gas analysis and determination of M plasma and P blood concentrations.

A baseline study was recorded before anesthetic induction (awake). Anesthesia was induced with either P or M (2 mg/kg) followed by an infusion of 100 µg.kg^{-1}.min^{-1}. Vecuronium (0.05 mg/kg) was administered and a manually controlled ventilation (FiO$_2$, 1.0) was instituted (FECO$_2$, 4-5%). Then, six series of measurements were made between 1 and 2.5, 3 and 4.5, 6 and 7.5, 9 and 10.5, 12 and 13.5 and 15 and 16.5 minutes. After the last of the data acquisitions the trachea was intubated and the patient was moved into the operating room.

All data are given as mean ± SD. Two factors repeated measures ANOVA, Scheffé F-test and Dunnett *t*-test were used for statistical analysis. P< 0.05 was considered significant.

Results: The main results are summarized in the table.

		awake	3 min	15 min
HR	P	71±13	73±11°°	68±11°
(b / min)	M	74±9	90±10‡	80±12†
MAP	P	99±17	85±16‡	80±15‡
(mmHg)	M	101±16	84±15‡	85±13‡
PCWP	P	6.1±2	2.6±2°°‡	3.1±2.9°‡
(mmHg)	M	6±1.9	5.2±1.8	5.5±1.7
thCI	P	3.14±0.65	2.41±0.64‡	2.42±0.83‡
(l.min^{-1}.m^2)	M	2.96±0.68	2.24±0.45‡	2.32±0.46‡
thSI	P	45.1±7.8	33.4±7.7°°°‡	36±8.7‡
(mlb^{-1}·m^2)	M	41.2±9.2	25±4.5‡	29.8±7.4‡
SVRI	P	31±5	34±7	33±8
((UI / m^2)	M	34±8	36±7	36±8
EF	P	55.7±5.6	56.9±7°°	57.5±7.9°°
(%)	M	54.4±6.1	46.3±6.5‡	46.4±6.3‡
EDV	P	141±22	129±17‡	130±17‡
(ml)	M	133±22	131±23	132±24
ESV	P	61±12	56±14°	56±15°
(ml)	M	61±12	70±14‡	71±14‡

mean±SD

°$p<0.05$;°°$p<0.01$;°°°$p<0.001$, compared P vs M at the same time

†$p<0.05$;‡$p<0.01$, compared to awake for the same group

Discussion: In CAD patients with good EF and PCWP < 12 mmHg, P and M anesthesia significantly decreased MAP and CI in the same degree. However, the mechanisms of reduced MAP and CI were different. In contrast to P, M did not decrease preload but it altered LV performance: EF decreased and ESV increased. Despite the relatively large decreases in MAP and CI seen in our patients, there was no evidence of development of myocardial ischemia with either P or M. But the mechanism of the arterial pressure reduction with M, is cause for concern in patients with altered left ventricular function.

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Title EFFECT OF NITROUS OXIDE ON FUNCTION OF COMPROMISED MYOCARDIUM WITH AFTERLOADING IN ANESTHETIZED DOGS

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Introduction. Controversy exists regarding the safety of nitrous oxide administration to patients with coronary artery disease. While experimental studies have suggested nitrous oxide to be deleterious (1). nitrous oxide causes no adverse effects in regions of compromised blood flow in patients with coronary artery disease (2). A previous study has shown that ischemic changes in regional myocardial function occur with increased afterloading caused by abdominal aortic cross-clamping (3). We wondered whether the addition of nitrous oxide would change the performance of a region of myocardium with compromised blood flow when the left ventricle was acutely afterloaded.

Methods. This study complies with the Animals (Scientific Procedures) Act of 1986 (U.K.). Eight premedicated mongrel dogs (wt. range 16-21 kg) underwent a left thoracotomy with halothane anesthesia in 66% N_2/33% O_2. The animals were instrumented so that left ventricular pressure, aortic pressure, coronary blood flow, and regional function (sonomicrometry) in the left anterior descending coronary artery (LAD)-supplied apical subendocardium were measured, as per a previously described method (1). A micrometer snare was placed around the LAD distal to the first diagonal branch and the coronary flow probe. A segment of the descending thoracic aorta was isolated, and a snare placed around it to perform acute partial aortic constrictions. Halothane was then discontinued, and the animals were given a 5 mg/kg loading dose of propofol followed by a 0.3 mg $kg^{-1}hr^{-1}$constant propofol infusion. The micrometer snare was then tightened slowly to critical LAD constriction, defined as the point where normal regional myocardial function remains yet there is a loss of reactive hyperemia to a 10 s coronary occlusion. Data were then collected 67% N_2 in O_2 and 67% nitrous oxide, replacing the N_2. In addition, the aorta was acutely constricted to raise systolic aortic pressure by approximately 40% with ventilation temporarily halted. Data with afterloading were obtained with N_2 and with nitrous oxide, and a single beast was analyzed in each stage. Extrasystolic or post-extrasystolic beats were excluded. Results were analyzed by paired t-test or Wilcoxon matched pair test, as appropriate. $P<0.05$ was considered significant.

Results. Data are presented as mean ± S.D. Acute aortic constriction caused similar increases in systolic pressure with N_2 and nitrous oxide (43.5% ± 11.3 vs. 45.6% ± 9.8, respectively, P=n.s.). However, a marked decrease in regional myocardial function occurred with afterloading during nitrous oxide administration, as evidenced by a significant decrease in SS (see Fig). A similar amount of PSS with afterloading was seen with N_2 and nitrous oxide (19.7 ± 10.4 vs. 22.0 ± 11.2, respectively, P=n.s.).

Discussion.The present study demonstrates that nitrous oxide markedly attenuates the ability of a compromised region of the left ventricle to respond to acute afterloading in the experimental setting. Thus nitrous oxide significantly alters the capability of compromised myocardial segments to react to acute afterloading stress. These results suggest that the use of nitrous oxide may significantly reduce the cardiac reserve of patients with coronary artery disease. This reduction of cardiac functional reserve capacity by nitrous oxide may be an important consideration during procedures likely to acutely increase arterial pressure.

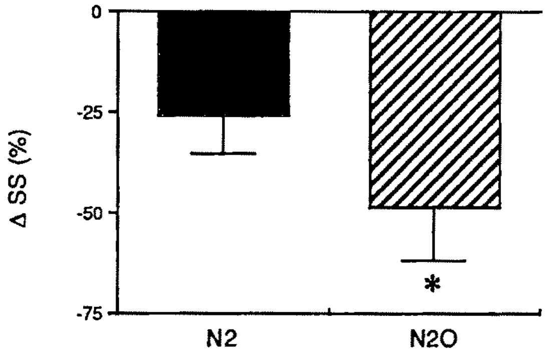

Figure: Comparison of the effects of 67% nitrogen (N_2) vs. 67% nitrous oxide (N_2O) on systolic shortening (Δ SS%). Δ SS% units are percentage change vs. normal loading conditions. * denotes $P<0.05$ by Wilcoxon test.

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Title: THE EFFECT OF PREOPERATIVE ANXIETY AND PREMEDICATION WITH MIDAZOLAM ON RECOVERY FROM AMBULATORY SURGERY

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Introduction: Patients who undergo ambulatory surgery may be anxious, yet, because of recovery considerations, are frequently denied pharmacologic control of their anxiety. We designed the following experiment to test whether the pharmacologic relief of anxiety affects various aspects of recovery.

Methods: Fifty-two consecutive consenting patients who were not currently receiving narcotics, anxiolytics, or antihypertensives; who were not hypertensive (systolic BP < 140); and who weighed less than 100 kg were enrolled in the study. Initially, patients completed the Hopkins Symptom Checklist (HSCL). Upon completion of this study, and blinded to the other results, we determined the mean value of the anxiety scale from the HSCL in order to segregate the patients into either a low or high anxiety group. In the preoperative holding area, in a blinded fashion, patients received either midazolam (M) 0.05 mg/kg (5mg/ml) or an equal volume of placebo (P). Practice and baseline measurements of all psychomotor tests were made prior to drug administration and anesthesia. A standardized anesthetic regimen was used. All postoperative measurements, except for the ability to open eyes and for orientation to time and place, were made every hour for 4 hours after the end of anesthesia. Measurements of all variables were made by observers unaware of preoperative medication.

Recovery and psychomotor skills evaluated were the ability to open and close the eyes, to know time, place and person, to stand and walk a straight line, and to take tests measuring perceptual speed, eso- and exophoria, finger tapping speed, and alternating tap. Pain intensity (visual analogue scale), and analgesic intake were also measured. Statistical analysis was performed using analysis of variance and all results are expressed as mean ± SD.

Results: Of patients with low anxiety, eighteen received placebo and sixteen received midazolam; ten anxious patients received placebo and eight anxious patients received midazolam. Patients who received midazolam took longer to open their eyes (P vs M: 9.64±5.60 min vs 13.75± 8.11 min) and took longer to become oriented (P vs M: 14.11± 8.28 min vs 22.29±15.46 min) after their anesthetic ($p<0.05$ for both). However, there was no significant difference according to drug administered or preoperative anxiety group in ability to stand or walk. In addition, time to discharge from the recovery room was not affected by the administration of midazolam. Eso- and exophoria, alternating tap, finger tapping speed, and perceptual speed were all significantly impaired after anesthesia (all $p=0.0001$). Midazolam caused more impairment overall than placebo for eso- and exophoria (P vs M: 6.60± 3.03 diopters vs 8.66± 3.80 diopters) ($p=0.0001$), and perceptual speed (P vs M: 62.53± 8.97 answers vs 59.14± 11.96 answers) ($p=0.008$); if the first two hours after anesthesia are excluded, the effect of midazolam on perceptual speed was not significant. Patients who were anxious and received midazolam performed better overall on the alternating tap test than anxious patients who received placebo; conversely patients who were not anxious and received placebo performed better on the alternating tap test than non-anxious patients who received midazolam ($p=0.002$) (not anxious: 91.30± 18.64 taps-P vs 74.89± 14.34 taps-M; anxious: 84.46± 14.99 taps - P vs 90.45± 23.43 taps-M). Pain decreased significantly in all patients over the four hours after anesthesia ($p=0.0001$). In patients receiving midazolam, overall pain was less (P 4.88± 1.88 vs M 4.03± 1.87) ($p=0.0045$), but the postoperative administration of narcotics was not affected by midazolam or level of anxiety. All patients felt more sedated after the anesthetic than before; however, the patients who felt anxious preoperatively felt less sedated postoperatively (not anxious-3.32± 2.29 vs anxious-2.37±1.59) ($p < 0.01$).

Discussion: Anxiety played a substantial role in recovery from anesthesia as measured by performance on the alternating tap test, and on the feeling of sedation. Patients premedicated with midazolam experienced less pain sensation postoperatively and, except in the first two hours, were not impaired during recovery. The effect of midazolam on esophoria, though, persisted up to four hours after the anesthetic. The improvement in performance of the most anxious patients after midazolam is similar to that seen after low dose alcohol where relief of anxiety is postulated to improve performance during psychomotor testing.[1] Premedication in anxious outpatients seems to have little deleterious and even some beneficial effects on recovery from surgery.

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Title: **THE EFFECT OF SLEEP DEPRIVATION ON PSYCHOMOTOR PERFORMANCE IN ANESTHESIA RESIDENTS**

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Introduction: That lack of sleep in house officers may affect their performance has for many years been a concern. Although anesthesia personnel typically are relieved after 24 hours of duty, many residents are required to work shifts as long as, or even longer than, 36 hours. The object of this study was to determine the extent of deterioration of psychomotor function in anesthesia residents who spend the night on call.

Methods: Six anesthesia residents were asked to volunteer for a study of the effects of a night on call on their ability to function. Before the volunteers were actually enrolled in the study, they were trained to use the test apparati to help prevent further learning of the tasks during actual testing. Psychomotor tasks were performed before the start of the operating room day (approximately 0630), and again the next morning. The residents were tested in two different sessions using a crossover design: once during a call session and once during a non-call session. Three residents were tested beginning with the morning prior to a night on call and three were tested beginning with the morning prior to a night not on call. Auditory and visual reaction time were determined by measuring the time required for the resident to press a button after hearing a sound or seeing a letter presented on a computer monitor. Coordination accuracy was measured by having the resident track a moving circle on a computer screen with a "mouse"; the score represents the mean distance between the cursor and the target during the test. The Profile of Mood States (POMS) was used to measure mood states because it is sensitive to transitory mood states, including fatigue.[1] Residents were told to rate the POMS according to the way they felt at that moment. Paired t-tests were used to compare the test results at equivalent time periods.

Results: No difference was seen in baseline performance at the beginning of the twenty-four hour period when the residents were either on or not on call. As expected, sleep time while on call was significantly less than when not on call (3.08 ± 0.5 vs 6.0 ± 0.4 $p<0.01$). At the end of the twenty-four hour period, visual reaction time and coordination accuracy were more impaired in residents when they were on call than when they were not on call. Auditory reaction time tended toward impairment, but scatter prevented this difference from being significant. As measured by the POMS, fatigue was markedly greater after a call period than a non-call period. The table shows results of the different tests, as well as those of a previous similar study where changes were measured one hour after volunteers consumed 1 g/kg of alcohol.

Table: Mean ± SD of different tests at the end of a 24-hour period not on call and on call. * indicates two-tailed significance of $p<0.05$ for the paired t-test. NM=not measured.

	Non-call	Call	Mean Diff	Mean Diff After Alcohol
Visual Reaction Time (sec)	0.31 ± 0.03	0.36 ± 0.06	0.047*	0.037*
Auditory Reaction Time (sec)	0.27 ± 0.03	0.30 ± 0.04	0.027	0.042
Coordination accuracy (pixels)	12.31 ± 1.48	13.80 ± 1.38	1.49*	1.79*
Fatigue	1.02 ± 0.74	1.79 ± 1.09	0.76*	NM

Discussion: In a previous study, these same psychomotor tests were used to assess performance after an oral dose of alcohol (1.0 g/kg). After one hour, with a blood alcohol level of 0.86 g/l (driving with a level of 1.0 g/l is illegal in many states), performance decrements were of the same order of magnitude as those observed in residents when a call period was compared to a non-call period. Although the relative change in sensation of fatigue by these residents was somewhat greater than the decrement in psychomotor function, the decrement in psychomotor function was about as great as that produced by mild inebriation with alcohol. Because the importance of adequate sleep for anesthesiologists has been recognized, their maximum work periods are often 24 hours. Our results suggest that the practice of relieving anesthesia personnel after a night on call may be important. However, further work with a greater number of residents, particularly with residents who have to work periods greater than 24 hours, is indicated.

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Title: EFFECTIVENESS OF PREMEDICATION IN ANXIOUS PATIENTS: DOES FENTANYL OR DIAZEPAM ALLAY ANXIETY?

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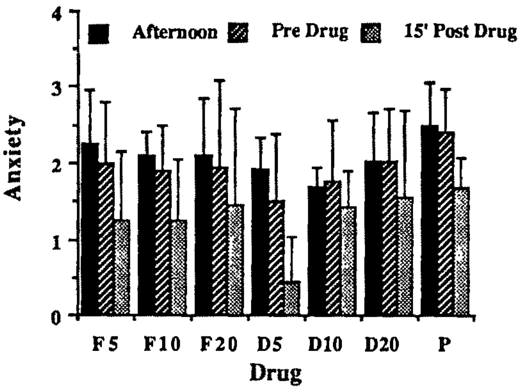
Introduction: The primary purpose for preoperative medication in adults is to allay anxiety but surprisingly little work has been performed to assess the effectiveness of premedicants in accomplishing this goal. We designed the following experiment to compare the effect of the premedicants diazepam or fentanyl to no premedicant in patients who were anxious preoperatively.

Methods: After this study was approved by our clinical investigation committee, we visited patients who were to undergo abdominal operations estimated to last between one and five hours on the afternoon before surgery. At that time, they were asked to complete the Profile of Mood States (POMS) to determine their level of anxiety.[1] The POMS was chosen because it is sensitive to momentary mood states, including anxiety; it is factor analyzed into the following ten subscales: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, Elation, Arousal, and Positive Mood. In a previous study of inpatients, we found that the average score on the POMS Anxiety scale the afternoon before surgery was 0.95.[2] Forty-two consecutive ASA I-II patients, aged 21 to 60 met the criteria for study inclusion: i) they were not currently receiving narcotics or anxiolytics, ii) they weighed less than 100 kg, iii) they had high anxiety levels as judged by a score of 1.25 or greater on the anxiety scale of the POMS, and iv) they agreed to participate. The patients were randomly assigned to seven groups to receive as a premedicant either 5, 10, or 20 mg diazepam; 50, 100, or 200 µg fentanyl; or saline placebo. The next day, when the patients were brought to the preoperative holding area, they again completed the POMS. An IV was started, their premedicant was injected IV, double-blind, and after 15 minutes they again completed the POMS. Blood pressure and heart rate were measured every five minutes from injection until the POMS had been completed for the last time. We used repeated measures analysis of variance to compare the changes in mood factors as measured by the POMS, at the three times the scales were administered, dividing the patients into groups according to premedicant. All values are expressed as mean ± S.D.

Results: 42 patients, whose average age was 35.4 ± 8.59 years and average weight was 66.1 ± 16.0 kg were studied. The groups did not differ in weight or age. Repeated measures analysis of variance revealed that the factors Anxiety, Arousal and Vigor decreased significantly and Elation and Positive Mood increased significantly from before to 15 minutes after drug administration without respect to drug administered (all factors $p<0.001$ except Positive Mood, $p<0.05$). Patients became relatively more fatigued with all doses of diazepam ($p<0.025$) and specifically with diazepam 20 mg ($p=0.001$) when compared with those receiving placebo. Blood pressure decreased significantly over the period from before to 15 minutes after injection ($p=0.01$). Neither fentanyl nor diazepam were more effective than placebo in reducing anxiety (figure).

Figure: Variation of Anxiety with time and drug. F5, F10, and F20 refer to fentanyl 50, 100, or 200 µg; D5, D10, and D20 refer to diazepam 5, 10 or 20 mg; P means placebo.



Discussion: This group of patients was selected because they were anxious. Although their average Anxiety score did drop significantly after 15 minutes in the preoperative holding area, their scores were still higher than an "average" group of inpatients in the preoperative holding area (1.09 ± 0.96).[2] Patients became more fatigued after diazepam, but not less anxious. Studies are continuing to determine if anxiety reduction begun sooner than 15 minutes before surgery, using either pharmacologic or psychotherapeutic means, might be more effective in reducing anxiety in the preoperative holding area.

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Title: REAPPRAISAL OF HEAT - MOISTURE EXCHANGER

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Introduction Despite many theoretical advantages of humidification of anesthetic gas, the role and method of choice of humidification in anesthesia remains uncertain. With the recent introduction of disposable heat-moisture exchanges (HME's), a paucity of information on the specific performace characteristics of various HEM's exists. Using an on-line humidity detector, based on the dry-wet bulb principle, with a fast response temperature sensor (0.1 sec. RT), we have reexamined the effectiveness in maintaining humidity and temperature of various commercially available HME's in clinical settings, and the relationship of the effectiveness of the HME's to the rate of fresh gas flow. The thermodynamics of the circle system have also been closely examined with or without HME.

Methods Following the study protocol approved by the institutional clinical investigation committee, adult patients undergoing general anesthesia with endotracheal intubation were selected for the study. Ventilation was set at 10 ml/kg of tidal volume at ventilatory rate of 10 breath/min. The pressure gradient across the HME and temperature of the circle system at 4 separate locations were also monitored. Tested HME include Humidivent I, Hemidivent II, Engstrom 1000, Siemens, Thermovent and Pall. For the HME comparison study, anesthesia and ventilation were maintained at 5000 ml/min of fresh gas flow (FGF) for 30 minutes. Baseline humidity was detected by a humidity sensor placed between the circle Y connector and the endotracheal tube. After baseline humidity was recorded, a randomly selected HME device was placed between the humidity sensor and the Y connector of the circle system and efficacy in maintaining humidity and temperature was examined. Following one set of measurements (20 minutes after), FGF was reduced in 1000 ml/min increments and the humidity status was examined. For the long-term durability study, an HME was selected randomly; the patients received 3000 ml/min of FGF. Room temperature was kept consistent at 22°C and was monitored by YSI524 temperature probe. Inspired temperature was also measured by YSI524 at 10 cm proximal to Y connector.

Results (1) The circle system gas temperature ranges between 19.5 to 27°C and depended on room temperature, duration of anesthesia and FGF. (2) All HEM's tested demonstrated significant preservation of the heat and moisture. The best HME demonstrated 9 degree inspiratory temperature difference across HME. (Table 1) (3) When HME was placed, change in the FGF flow rate did not effect temperature and humidity of the gas patient inspirated significantly. (4) Extreme low FGF (Table 11) (closed-circuit) without HME demonstrated high relative humidty, but inspired gas temperature remained relatively low because of low room temperature, therefore, water content of inspired gas remained lower than during use of HME. (5) Up to 4 hours long-term evaluation, HME provides consistent performance except in two occasions; one with Humidivent I and one with Engstrom. A gradual decline in performance was seen after three hours of usage in these two HME's. There was no significant rise in pressure gradient across the HME over the time. (6) With or without HME, inspired temperature (10 cm proximal to Y connector) did not change with time except FGF 1000 ml/min or lower.

Discussion With fast response temperature probes and newly constructed humidity detectors, inspiratory and expiratory temperature and humidity changes can be detected breath by breath. Our evaluation of HME's clearly demonstrated HME's significant capability to preserve heat and moisture, as indicated by a significant temperature rise in inspired gas across the HME. These results seem quite different from the previous publications.[1,2] The differences may attribute to the difference in the test paradigm (in vitro vs in vivo), room temperature and sensitivity of the dector. With extremely low FGF (closed-circuit anesthesia), we demonstrated that high relative humidity can be maintained in the inspired gas, but inspired gas temperature did not rise significantly. Hence, absolute humidity stayed relatively low and seldom exceeded 25 mg H_2O/L. This study did not define the best method in humidification, but it indicates significant contributions from HME in preservation of heat and moisture.

Table 1

HME Performance
(2000 ml/min FGF Room Temp 22.4±0.2°C)
(mean ± 1 S.D. n = 6)

	Insp. T. prior to HME (C°)	Insp. T. After HME (C°)	Exp. T. (C°)	$H_2$0 cont. (inspired) (mg$H_2$0/L)
Humidivent I	22.82 ±0.3	29.65 ±0.86	32.86 ±0.91	24.4 ±0.8
Humidivent II	22.78 ±0.2	31.35 ±0.89	33.40 ±1.01	27.4 ±0.7
Engstrom 1000	22.79 ±0.2	30.78 ±1.36	33.15 ±0.88	26.3 ±0.7
Siemens	22.79 ±0.3	30.15 ±0.77	32.87 ±0.89	25.2 ±0.7
Thermovent 1200	22.82 ±0.3	31.27 ±0.89	33.34 ±0.89	27.2 ±0.7
Pall	22.80 ±0.3	30.06 ±0.85	33.21 ±1.07	25.1 ±0.8

Table II

Measured Inspired Absolute Humidity Without HME
(30 min. after induction of anesthesia)

Fresh Gas Flow Rate (ml/min)	Absolute Humidity (mg$H_2$0/L)
5000	12.96 ± 1.71
3000	15.05 ± 2.45
2000	17.22 ± 1.80
500	18.87 ± 1.28

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Title: **HYPOXEMIA OCCURS INTERMITTANTLY AND SIGNIFICANTLY WITH NITROUS OXIDE LABOR ANALGESIA**

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INTRODUCTION: Pregnant patients have a higher tendency for hypoxemia, due to a combination of both increased oxygen consumption and decreased functional residual capacity (FRC). It has been shown that contractions cause hyperventilation, which is followed by intercontraction hypoventilation. The intercontraction hypoventilation can cause further arterial oxygen desaturation.(1)

We hypothesize that the use of nitrous oxide in the laboring parturient provides an ideal model during which diffusion hypoxia can occur during nitrous oxide inhalation. In this study, we demonstrate clinically significant between contraction hypoxemia occurring when nitrous oxide is inhaled during contractions. In comparison, no oxygen desaturations are seen with continuous epidural labor analgesia.

METHODS: Human Subjects Committee approval and individual patient informed consent was obtained for this study. Nine unmedicated, healthy women in active labor, requesting labor analgesia, were studied. Patients received either a) nitrous oxide analgesia (n=4, 50% nitrous oxide during labor contractions) or b) epidural analgesia (n=5, 0.25% bupivicaine bolus, followed by a continuous 0.125% bupivicaine infusion). Oxygen saturation was monitored by noninvasive pulse oximetry and uterine contractions were monitored by tocometer.

After establishing effective analgesia (Visual Analog < 5), arterial saturation was continously monitored. For ten consecutive contractions, the exact time of desaturation (temporal relationship to contraction) and degree of desaturation were quantified when uterine contractions were occuring every two to three minutes. Apgar scores and venous cord pH were also recorded to compare neonatal outcome. Statistical analysis was performed by Student's t-test ($p < 0.05$ considered significant).

RESULTS: The two groups were not significantly different with respect to maternal age or neonatal outcome (Apgar scores, venous cord pH, $p > 0.05$). Baseline oxygen saturation/desaturation patterns were not different prior to the establishment of either epidural or nitrous oxide analgesia.

However, following the establishment of effective pain relief, the nitrous oxide group demonstrated significant episodes of maternal hypoxia almost after every contraction during which N_2O was inhaled. Figure 1 is a typical example.

Table 1 shows the time from maximal uterine contraction to the maximum of arterial desaturation. Table 1 also shows the maximal decrease in postcontraction arterial saturation in the nitrous oxide labor analgesia group. None of the patients who received epidural analgesia showed any significant episodes of hypoxemia, and in fact attenuated any preexisting minor oxygen desaturations which might have occurred.

FIGURE 1: Laboring Patient Receiving Nitrous Oxide

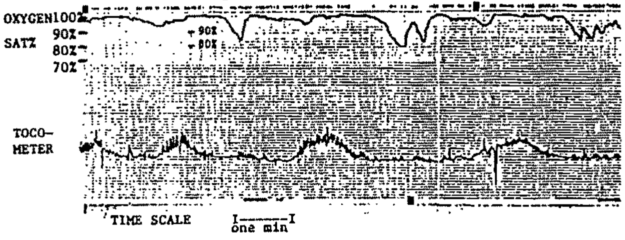

TABLE 1

Patient	Mean Time (sec) Maximal Uterine Contraction to Maximal O_2 Desat.	Mean Maximal Oxygen Desat. Value for 10 Contractions(%)
1	62 ± 10	80 ± 6
2	48 ± 8	82 ± 8
3	55 ± 10	90 ± 2
4	71 ± 20	86 ± 4
MEAN	59 ± 13	84 ± 5

DISCUSSION: We have demonstrated clearcut clinically significant , intermittant hypoxemia following nitrous oxide inhalation for labor analgesia. Deckardt et al (2) reported a decreased "mean" oxygen saturation in primiparas receiving meperidine and nitrous oxide at irregular intervals vs primiparas receiving epidural analgesia. The nitrous oxide and narcotics were given at infrequent and irregular intervals, and the temporal relationship between the analgesia, uterine contraction and oxygen desaturations were not specified. The authors theorized that the patients receiving nitrous oxide/meperidine had more pain and that the oxygen saturations were pain dependent.

All patients included in this study reported good pain relief. There is a consistent pattern of hypoxemia which occured in the nitrous oxide group. We theorize that the most likely explanation is through the phenomenon of diffusion hypoxia. Active hyperventilation during contractions cause a rapid upatke and distribution nitrous oxide. At the end of the contraction, patients breathe room air during which the outward diffusion of nitrous oxide lowers the alveolar partial pressure of oxygen. This leads to hypoxemia. The term patient is a perfect set up for diffusion hypoxemia in that the term patient has a very small (reduced FRC) and homogeneous (positive end tidal CO_2 to P_aCO_2 gradient) lung.(3)

In this study, no fetal heart rate abnormalities or differences in neonatal outcome were found. However, in the presence of compromised placental blood flow, or in the parturient with compromised pulmonary function, the fetal effects from these episodes of hypoxemia may be very significant. The use of nitrous oxide labor analgesia delivered in this manner in such high risk obstetrical patients may be contraindicated. Other patients should require pulse oximetry for closer observation and/or oxygen supplementation between contractions.

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Title: NEUROMODULATION OF SPASTICITY FOLLOWING SPINAL CORD INJURY WITH INTRATHECAL BACLOFEN.

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INTRODUCTION: Recently, Penn et al (1) and Muller et al (2) reported their experiences with intrathecal baclofen (IB) for spasticity control in patients with spinal cord injury (SCI), multiple sclerosis and head injury. Their findings demonstrated that IB produced predictable and titratable reduction of spasticity when administered by infusion reservoir. This study was undertaken to comprehensively evaluate the effects of IB in SCI patients with severe spasticity. Preliminary results are described.

METHODS: Institutional Research Committee approval and informed consent were obtained. Four patients (Cervical=2, Thoracic=2) with stable, non-progressive SCI (> 6 mos. duration) were studied. Each patient had severe tonic and phasic spasticity of the lower extremities and trunk musculature with or without pain that significantly interfered with daily living, and was not amenable to control using oral baclofen, diazepam or dantrolene). Spasticity and pain medications were discontinued and baseline clinical and laboratory evaluations completed, including grading of spasticity (Ashworth Scale), reflexes, pain (VAS), functional independence and mobility, evoked potentials, poly-EMG, Cybex and cystometrography. In Stage 1, a 23g polyethylene catheter was inserted via a lumbar 20g Tuohy needle 2-3 cms intrathecally and connected to an external pump. A continuous infusion of IB was commenced at an initial rate of 50 mcg/day, increased every 12 hours in 50 mcg increments until optimum spasticity control was obtained. For one 12-hour infusion period, placebo (normal saline) was substituted for baclofen. Baclofen and placebo were administered in a double-blind fashion, and follow-up clinical evaluations (spasticity, pain, side-effects) were performed every 12 hours. Assessment of functional independence, mobility and laboratory evaluation procedures were repeated once optimal control of spasticity was achieved. In Stage 2, a programmable subcutaneous infusion reservoir (Medtronic Model 8611H) connected to a lumbar intrathecal catheter, was surgically implanted with general anesthesia, and percutaneously filled with B. The infusion rate selected was equal to that determined during Stage 1 for optimal spasticity control. Following hospital discharge, patients were seen monthly on an outpatient basis, which included re-filling the reservoir with B and clinical assessment. The daily dosage was adjusted by changing the concentration of B and the pump flow rates using computerized telemetry.

RESULTS: Four patients underwent Stage 1, with 3 patients undergoing pump implantation. All 4 patients responded positively to IB, demonstrating negative placebo responses. For Stage 1, the optimal daily baclofen dosage ranged from 35-375 mcg/day. Quadraplegic patients required a higher daily dosage than paraplegic patients. Beneficial effects on spasticity included titratable reduction of both tonic and phasic components, decreased discomfort and improved sleep. Functional gains included improved wheelchair balance, ambulation and transfers, increased independence and selfconfidence. Decreased upper extremity spasticity (n=1) and improved pulmonary function (n=1) were also observed. Side-effects included mild hypertension and persistent burning lower extremity dysesthesia (n=1). Clinical observations of spasticity were confirmed by laboratory testing, i.e., low amplitude voluntary activation of spasticity in response to volitional maneuvers, passive stretch and cutaneous stimulation. Lower extremity myotatic reflexes were decreased. Neurophysiologic effects on ascending spinal cord transmission and/or brainstem function were not observed during infusion of IB. Cystometrography revealed increased bladder compliance (n=3) and increased detrusor contraction (n=1). During Stage 2, patients required small increased daily dosages of baclofen (25-50 mcg/day) following pump implantation. Continuous infusion modes were used and pump flow rates were set at 0.6 ml/day requiring monthly refills.

DISCUSSION: These preliminary results demonstrate that IB produces efficacious control of spasticity associated with incomplete SCI. Baclofen, a p-chlorophenyl derivative of GABA, has been used effectively via the oral route for spasticity management. However, daily dosage is limited by central side-effects. The continuous intrathecal infusion method, while providing adequate spasticity control, permits the use of small amounts of B, thus minimizing side-effects. However, long-term administration of IB may be associated with tolerance phenomena (1). Experimental data have shown that baclofen antagonizes the excitatory neurotransmitter S-glutamate (3). Further studies are in progress.

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TITLE: **EPIDURAL MORPHINE FOLLOWING ANTERIOR CRUCIATE LIGAMENT REPAIR: A COMPARISON WITH PATIENT-CONTROLLED INTRAVENOUS MORPHINE**

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Introduction: The management of postoperative pain is significantly improved with the application of either epidural narcotics or patient-controlled analgesia (PCA). Neither technique is without risk or undesirable side-effects. To compare the management of postoperative pain using epidural morphine with PCA morphine, we reviewed 47 consecutive cases involving repair of the anterior cruciate ligament.

Methods: This retrospective review was undertaken with institutional approval. Initial PCA parameters included a morphine incremental dose of 1 mg, a lockout interval of 8 minutes and a rolling 4 hour maximum of 30 mg. If pain persisted the incremental dose was increased to 1.5 mg and/or the lockout period decreased to 6 minutes. The initial epidural morphine dose, 4 mg, was administered 1 hour before completion of surgery. Subsequent morphine doses, typically 4-6 mg, Q6-8 hrs, were adjusted as needed for patient comfort.

The quality of analgesia achieved and the incidence of side-effects were noted on daily postoperative visits throughout recovery. For this report we considered the following information: (1) the effective 24 hour morphine dose with each technique; (2) patient estimates of incisional pain both at rest and with ambulation using a 0 to 10 verbal analogue scale (0="no pain" and 10="the most severe pain possible"); (3) the incidence and severity of side-effects including pruritis, nausea and urinary retention on a 0 to 3 scale (0=none; 1=mild; 2=moderate; 3=severe); (4) the incidence of respiratory depression (RR < 8).

Statistical analysis of parametric data used the chi-squared test; the Mann-Whitney test was used for nonparameteric data. Statistical significance was defined as $p < 0.05$.

Results: Postoperative pain was managed with epidural morphine in 30 patients and with PCA morphine in 17 patients. There were no differences in the demographic data, but patients receiving epidural morphine required a significantly lower 24 hour dosage (Table 1). Compared to patients receiving PCA morphine, the epidural morphine group reported significantly lower pain scores both at rest (0.7 ± 1.1 vs. 3.4 ± 2.1, $p < 0.01$) and with ambulation (3.2 ± 2.1 vs. 6.1 ± 2.1, $p < 0.01$). Figure 1 shows the distribution of pain scores. Although patients receiving epidural morphine did have a significantly higher incidence of moderate urinary retention, there were no significant differences with respect to the incidence of pruritis or nausea (Table 2). No respiratory depression was noted in either group.

Discussion: Patients presenting for repair of the ACL represent a healthy surgical population undergoing a single procedure expected to cause severe pain. The relatively young age of these patients tends to eliminate previously described pain modifiers, such as old age, chronic pain and learned helplessness (1).

Early joint mobilization following certain orthopedic procedures, currently favored by orthopedists, may be limited by severe pain. Previous studies have not distinguished between pain at rest and with movement. We found that epidural morphine provided more profound analgesia under both circumstances. The higher incidence of moderate urinary retention did not cause major clinical concern given the greater analgesic relief provided by epidural morphine. If greater patient comfort permits earlier mobilization, a more rapid recovery may ensue.

Reference: (1) Ferrante FM et al. Anesth Analg 1988; 67:457-461

Table 1: Patient Characteristics

	Epidural	PCA
Sex (m:f)	14 : 16	11 : 6
Age (years)	25 ± 6	24 ± 7
24 Hour Dosage (mg)	12 ± 6	64 ± 24*

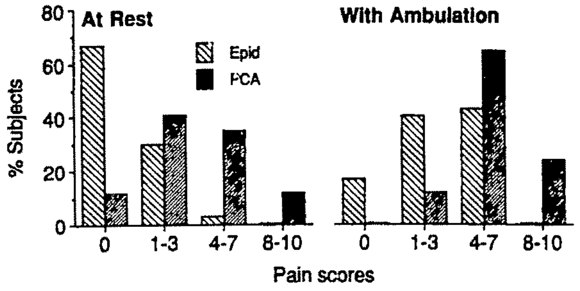
Values expressed as mean ± S.D.; * $p < 0.05$

Table 2: Incidence of Side Effects

	Zero	Mild	Mod.	Severe
PCA (n=17):				
Pruritis	65%	18%	6%	11%
Nausea	47%	41%	12%	0%
Urinary Ret	76%	6%	6%	12%
Epidural (n=30):				
Pruritis	27%	40%	23%	3%
Nausea	30%	23%	23%	23%
Urinary Ret	47%	0%	43%*	10%

* $p < 0.05$

Figure 1: Distribution of Pain Scores



TITLE: **TERROR IN THE ICU: PARALYZED WITH PAIN**

AUTHORS: K. A. Loper, M.D., S. Butler, M.D., M. Nessly, B.S., and L. Wild, R.N., M.S.

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Introduction. Chemical paralysis has been commonly mistakenly for a calm and painless state. One study involving a community hospital's Intensive Care Unit (ICU) reported that pancuronium was administered to 48 of 50 ventilated patients, often without concomitant sedatives or narcotics (1). This led *Lancet* to criticize such practice as callous therapeutic mismanagement (2). Yet the morbidity conferences at our institution continue to present cases of ICU patients whose only medication was a neuromuscular blocker. This prompted us to survey the pharmacological beliefs of the ICU staff.

Methods. With institutional approval, a questionnaire was mailed to 112 medical/surgical housestaff and 258 intensive care nurses. The survey requested the evaluation of several drugs for their effect on agitation, analgesia and anxiolysis. We chose medications commonly used in conjunction with ventilated patients. These included the narcotics fentanyl, meperidine and morphine; the benzodiazepines diazepam, lorazepam and midazolam; and the neuromuscular blockers pancuronium and succinylcholine. Respondents were requested to leave the space blank if they were not familiar with a drug's effect.

Relative frequencies based on the total number of respondents were used to calculate the rate of "unfamiliarity." Adjusted frequencies based on the number of respondents claiming knowledge of a medication were used to determine "endorsement." Responses from physicians were compared to nurses using the chi-squared test with continuity correction. Statistical significance was defined as $p < 0.05$.

Results. There were 122 respondents (33%), comprised of 84 nurses (36%) and 28 physicians (26%). The narcotics were correctly identified as analgesic agents without a direct effect on either agitation or anxiety.

The neuromuscular blockers were widely believed to be effective treatment for agitation (Figure 1). Compared to physicians, a significantly greater proportion of nurses endorsed the use of paralytic agents in the management of agitation ($p < 0.01$). Many physicians and nurses incorrectly thought that the neuromuscular blockers are analgesic (Figure 2). The majority of nurses and physicians incorrectly thought that the benzodiazepines provide analgesia (Figure 3). In this case a significantly greater proportion of physicians, as compared to nurses, believed that the benzodiazepines are analgesic ($p < 0.01$).

Discussion. Neuromuscular blockers are commonly administered in the critical care setting, yet there is little information regarding the appropriate use of these potent agents, or of concomitant sedatives and narcotics. The paralytic agents have no sedative or analgesic action. Benzodiazepines have no analgesic effect. So while chemically paralyzed patients may be heavily sedated, they may still experience pain.

There were serious misconceptions regarding the effects of neuromuscular blockers and benzodiazepines amongst the ICU staff at our institution. In response to this unsatisfactory situation we have developed an educational program. The program addresses the pharmacology of the neuromuscular blockers, narcotics and sedatives commonly administered in the ICU. The alert patient requires constant assurance that the paralysis is drug-induced and not permanent. The components of a drug regimen must be linked together to ensure patient comfort.

Therapeutic mismanagement is borne of clinical misconception which may cause patients to needlessly suffer. We present this study to encourage other hospitals to examine their staff's use of neuromuscular blockers in the ICU. Education promotes the appropriate use of these agents. The goal is optimal patient care.

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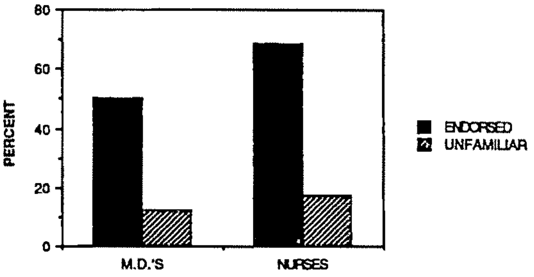

Figure 1: Pancuronium for Agitation

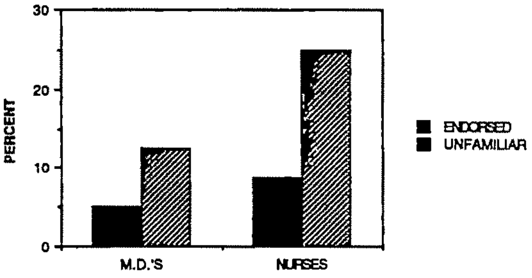

Figure 2 : Pancuronium for Analgesia

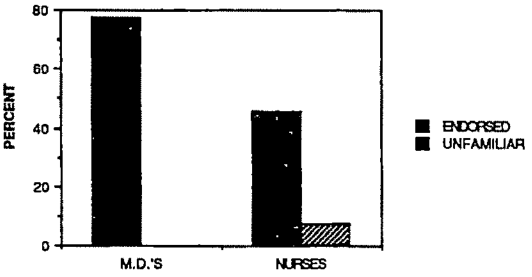

Figure 3: Diazepam for Analgesia

TITLE: **CHANGES IN LACTATE LEVELS WITH DECREASED OXYGEN DELIVERY AND OXYGEN CONSUMPTION UNDER ANESTHESIA.**

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Introduction: The blood lactate level reflects the adequacy of cellular oxygen supply in relationship to demand. When the cells are forced to resort to anaerobic metabolism during periods of inadequate oxygen supply, lactate is the end product of glycolysis. The liver can process and clear large lactate loads if it is perfused while other tissue beds are not, but a new steady state blood lactate level will result relatively rapidly.(1) Decreased hepatic perfusion/lactate utilization will also yield higher blood lactate levels.(1,2) We hypothesized that if cellular metabolism during the conduct of general anesthesia was inadequate with either oxygen delivery (DO_2) below 330ml/min/m^2 (3) or with low levels of oxygen consumption (VO_2) (4), then lactate levels should rise significantly if patients' oxygen delivery/consumption remained low for an extended period of time.

Methods: Institutional approval was obtained and informed written consent given by 9 hemodynamically stable patients undergoing cardiac or major abdominal surgery. All patients had preoperative lactate levels within normal limits. Patients were premedicated with a benzodiazepine and/or narcotic. A pulmonary artery catheter was placed under local anesthesia. The patients were induced with a combination of pentothal, sufentanil, and pavulon. Anesthesia was maintained with sufentanil and/or <.3 MAC potent inhalation agents. Approximately ten minutes after induction and before surgery began, hemodynamic variables were measured and arterial and mixed venous blood gases were drawn. Repeat determinations were made each hour prior to initiation of cardiopulmonary bypass or until conclusion of the abdominal surgery. No data points were obtained during periods of volatile hemodynamics. Oxygen delivery was calculated as cardiac index x arterial oxygen content. Oxygen consumption (VO_2) was calculated utilizing the Fick equation. A Yellowsprings 23L whole blood lactate analyzer was employed to measure lactate levels. Linear regression was used to evaluate the data.

Results: Nineteen data points with an oxygen delivery of less than 330ml/min/m^2 were identified. (Table 1). Changes in blood lactate levels over each hour were plotted against DO_2 (R^2=.14,p=.11) and VO_2 (R^2=.16,p=.09) values obtained at the end of each hour time period.

Discussion: Our data suggest that the "critical" level of DO_2 defined by Shibutani, as well as Waxman's finding of a significant inverse relationship between lactate and VO_2 are not applicable to all anesthetized patients. Shibutani suggested that VO_2 declined in a linear relationship with decreasing DO_2 below 330ml/min./m^2. The implication was that oxygen delivery was insufficient for appropriate aerobic cellular metabolism under anesthesia. The natural extension of this assumption was that if aerobic metabolism was insufficient then the cell would be utilizing anaerobic pathways to meet its energy needs. If this were the case, then blood lactate levels should rise when DO_2 and VO_2 fell. Waxman postulated the existence of an intraoperative "oxygen debt" proportional to decreases in VO_2 and linearly related to blood lactate levels. Our small sample size and the near significance of the p values prevents us from ruling out a possible relationship between the change in blood lactate levels and markedly diminished DO_2 and VO_2. However, the poor correlation coefficients when the change in blood lactate levels is plotted against DO_2 and VO_2 suggest a complex interplay of confounding factors such as temperature, anesthetic depth and interpatient variation. Therefore, in the clinical arena, it is hard to interpret the meaning of any particular value of DO_2 or VO_2 in a hemodynamically stable anesthetized patient. In addition, despite the very low values of oxygen delivery and consumption recorded in these patients, absolute lactate levels were never elevated enough in any of these 9 cases to be clearly outside normal limits.(1) This fact may indicate a limited clinical significance of following low DO_2 and VO_2 while an anesthetized patient is hemodynamically stable.

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DO_2 (ml/min/m^2)	VO_2 (ml/min/m^2)	Lactate (mmol/L)	Change in Lactate Over 1 Hour (mmol/L)
317	85	.6	0
240	68	.8	.2
322	73	1.3	.5
283	67	1.2	-.1
307	66	1.1	-.1
232	47	1.8	.5
200	51	1.6	.2
238	64	1.3	-.3
182	54	.6	.1
250	39	1.2	.5
209	52	1.1	-.1
143	45	1.6	.7
209	61	.3	0
248	49	1.1	.1
224	56	1.2	.1
280	46	.5	-.1
192	41	1.3	.4
183	36	1.3	0
160	39	2.0	.7

Title: **The Effects of Induction of Anesthesia**
on Mixed Venous and Peripheral Venous Oxygen Saturations

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Introduction: Measurement of mixed venous oxygen saturation (SvO2) is a useful indicator of the adequacy of tissue oxygenation in many critically ill patients.[1] As oxygen delivery (DO2) decreases or tissue oxygen consumption increases (VO2), SvO2 will decrease (i.e. SvO2 varies directly with DO2). A drop in SvO2 can therefore serve as a marker for impending tissue ischemia.

SvO2 is a flow weighted average of the blood returning from all perfused tissues. Abnormalities in microcirculatory autoregulation which occur in such states as septic shock, create a maldistribution of blood flow so that some tissue beds receive excessive flow while other tissue beds are underperfused and hypoxic. When blood flow maldistribution is present, a normal or elevated SvO2 may be measured while systemic oxygen needs are not being met. Several studies[2,3,4] have noted the lack of correlation between SvO2 and DO2 during general anesthesia. This suggested to us that general anesthesia might also produce a maldistribution of blood flow, explaining the relative independence of SvO2 from DO2. Support for this hypothesis was provided by France et.al.[5] who noted that under general anesthesia peripheral venous oxygen saturations were similar to arterial oxygen saturations (93.7% versus 96.1%).

We examined the effect of anesthetic induction on oxygen delivery and simultaneously measured peripheral venous and mixed venous blood gases. If maldistribution occurred, a differential change in peripheral and mixed venous oxygen saturation following induction of anesthesia would be seen.

Methods: Institutional approval was obtained and written informed consent given by 8 hemodynamically stable patients about to undergo cardiac surgery. Patients were medicated with a benzodiazepine and/or narcotic before induction. Patients were all given 2.5 liters/minute oxygen via nasal cannula and a pulmonary artery (PA) catheter was placed under local anesthesia. Three ml's of blood were discarded prior to obtaining the mixed venous blood sample. An antecubital or large wrist vein in an arm without an intravenous line was used to draw the peripheral blood gas. Anesthesia was induced with a combination of pentothal, pancuronium, and sufentanil. No inhalation agents were used. Approximately ten minutes after induction and before surgery began, repeat peripheral and mixed venous blood gases were obtained. The blood samples were analyzed on a 282IL co-oximeter and 1303IL blood gas analyzer. Two-tailed paired t-tests using the Bonferroni correction were used to evaluate the data.

Results: Following induction of anesthesia, SvO2 increased from 68±4% to 76±4% (NS). Peripheral venous saturation increased from 64±4% to 86±3% ($p<0.05$). There was a significant difference between the change in peripheral venous saturation (21.1±5.3%) compared to the change in SvO2 (7.5±2.7%) ($p<.05$) (Figure 1) Hemodynamic measurements before and after induction of anesthesia are summarized in Table 1.

Discussion: We have demonstrated that following induction of anesthesia with intravenous agents in hemodynamically stable patients, a differential change between mixed venous and peripheral venous oxygen saturation occurs. Highly saturated peripheral venous blood could mix with venous blood with decreased oxygen saturation returning from ischemic regions, producing a normal or elevated SvO2. Under these circumstances, a decreased SvO2 would be a late indicator of insufficient oxygen delivery and tissue hypoxia.

Determining the adequacy of tissue perfusion during surgery is difficult. Dramatic decreases in cardiac output, DO2 and VO2 can occur during general anesthesia as seen in our patients. The reduced VO2 may reflect inadequate tissue oxygenation or reduced oxygen need. The value of SvO2 as a measure of the adequacy of perfusion in anesthetized man is uncertain, as impaired oxygen utilization during anesthesia and surgery has been previously demonstrated.[2,6] Our results suggest that an anesthetic induced maldistribution of blood flow could account for the maintenance of normal SvO2's despite concomitant tissue hypoxia.[2,3,4] Intraoperative measurement of a normal or elevated SvO2 may give the anesthesiologist a false sense of security regarding the adequacy of tissue oxygenation.

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FIGURE 1

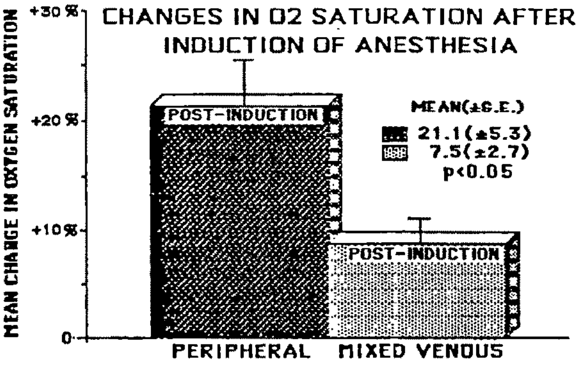

TABLE 1	PRE-INDUCTION	POST-INDUCTION
Cardiac Index (liters/min/m^2)	3.0±0.2	2.1±0.1
Mean Arterial Pressure(mmHg)	95±3	69±5
Systemic Vascular Resistance (dynes x cm x sec^{-5})	1313±115	1317±150
DO2 (ml/min/m^2)	461±44	313±28
VO2 (ml/min/m^2)	118±7	64±8
Oxygen Extraction Ratio (VO2/DO2)	28±4	22±4

TITLE: OXYGEN DELIVERY UNDER ANESTHESIA: A PROSPECTIVE EVALUATION OF 330ML/MIN/M^2 AS A "CRITICAL" VALUE.

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INTRODUCTION: Measurement of oxygen delivery (DO_2) and oxygen consumption (VO_2) has been proposed as an indicator of the adequacy of tissue oxygenation in the anesthetized patient. A "critical" DO_2 <330ml/min/m^2 has been suggested as a threshold below which VO_2 and presumably essential cellular metabolism decreases. Keeping O_2 delivery above 330ml/min/m^2 during cardiac surgery has been suggested.(1) We examined the change in O_2 consumption in a subset of patients who decreased their O_2 delivery below 330ml O_2 delivery/min/m^2. We also sought to address the question of whether there is a dependence of O_2 consumption on O_2 delivery under anesthesia.

METHODS: Institutional approval was obtained and informed written consent given by 8 hemodynamically stable patients undergoing cardiac surgery. Patients were premedicated with a benzodiazepine and /or narcotic. A pulmonary artery(PA) catheter was placed under local anesthesia. The patients were induced with a combination of pentothal, sufentanil, and pavulon. Anesthesia was maintained with sufentanil. No inhalation agents were used. Approximately ten minutes after induction and before surgery began, hemodynamic variables were measured and arterial and mixed venous blood gases were drawn. Repeat determinations were made each hour prior to initiation of cardiopulmonary bypass. No data points were obtained during periods of volatile hemodynamics. The blood samples were analyzed on a 282IL co-oximeter and 1303IL blood gas analyzer. Linear regression was used to evaluate the data.

RESULTS: Seven of eight patients had one or more determinations of O_2 delivery below 330ml/min/m^2 prior to initiation of cardiopulmonary bypass. The highest and lowest DO_2 values for these seven patients were used. Twelve of the fourteen data points were below the "critical" value. A linear regression was performed and r^2 was determined to be 0.01. (p=.72,NS)(Fig.1)Each individual patient was also evaluated. Only three of the seven patients decreased their oxygen consumption with concomitant decreases of their O_2 delivery in the range below 330ml/min/m^2. Three patients had no change and one had a slight increase in oxygen consumption.(Table 1,Fig. 2)

DISCUSSION: Given our results, it is hard to justify a strict adherence to the concept of maintaining a certain minimum oxygen delivery for all anesthetized patients undergoing cardiac surgery. We can neither confirm nor rule out a dependence of O_2 consumption on O_2 delivery during a narcotic based anesthetic. There are many factors in the clinical arena that may affect metabolic rate and VO_2 besides DO_2, such as changing levels of surgical stimuli and anesthetic depth. Furthermore, the effect of decreasing temperature during the pre-bypass period may also account for a decreased delivery being coupled with a decreased oxygen consumption in some patients. (In this group of patients, the greatest temperature difference between paired data points was 1.3°C.) In contrast to previously published papers(1), we did not weight our linear regression with different numbers of data points for different patients. We found no predictable decrease in VO_2 with decreased DO_2. Therefore, we conclude that there is no simple, reliable, absolute "critical" value of DO_2 for all patients undergoing cardiac surgery.

References:

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	Data Point 1		Data Point 2	
Patient	DO_2	VO_2	DO_2	VO_2
1	198	53	182	54
2	242	43	314	45
3	352	37	142	45
4	253	104	208	61
5	308	92	223	56
6	457	53	279	45
7	210	41	160	38

VO_2 VS DO_2<330 ML/MIN/M^2

Figure 1

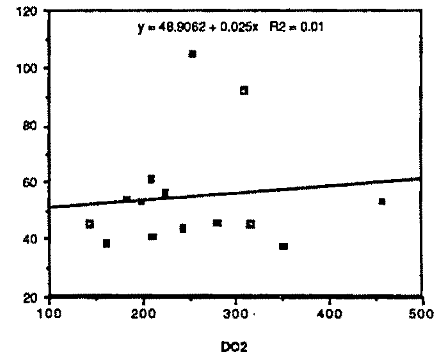
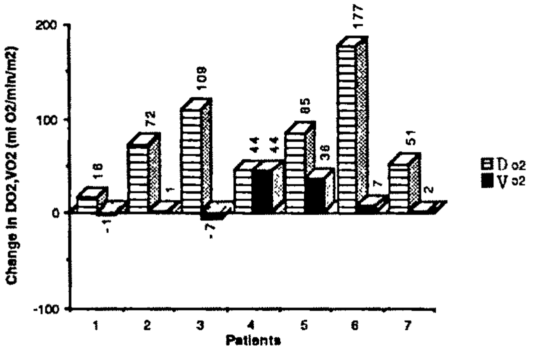


Figure 2, Individual Responses When DO2 Decreases Below 330ml/min/m2



Title:

DOXACURIUM CHLORIDE PHARMACOLOGY DURING NARCOTIC, ISOFLURANE AND HALOTHANE ANESTHESIA

Authors: D.P. Lynam, M.D., J.E. Caldwell, F.F.A.R.C.S. and R.D. Miller, M.D.

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Introduction: Doxacurium chloride is a new, long acting, nondepolarizing neuromuscular blocking drug (1) that is currently undergoing clinical investigation. Previously, the dose-response curves for doxacurium chloride were defined and compared in patients receiving one of the following three anesthetics: N_2O/isoflurane, N_2O/halothane or N_2O/narcotic (2). In the present study, the estimated ED_{95}, derived from these three subgroups, was administered as a single bolus dose to evaluate the onset, depth, and duration of twitch suppression produced by this drug.

Methods: After signing an informed consent statement, approved by our committee on Human Research, a total of 27 patients were studied. All patients were either ASA physical status I or II, were between the ages of 18 and 70 years, and had no major organ system disease. Following premedication with diazepam 10 mg P.O. or midazolam 0.02 - 0.07 mg/kg I.V., the patients were randomized to receive either a N_2O/narcotic (n=9), a N_2O/isoflurane (n=9) or a N_2O/halothane (n=9) anesthetic. General anesthesia was induced in the N_2O/narcotic group with the administration of thiopental (1-5 mg/kg I.V.) and either fentanyl (2-12 µg/kg I.V.) or morphine sulfate (0.1-0.2 mg/kg I.V.). It was then maintained with N_2O (60-70%) and with intravenous doses of either fentanyl, morphine sulfate and/or thiopental as required. In the inhaled anesthetic groups, anesthesia was induced with thiopental (1-5 mg/kg) and maintained with 60% N_2O and isoflurane or halothane at an end-tidal concentration that approximated 1.25 MAC as measured by mass spectrometry. Endotracheal intubation was accomplished without the use of a neuromuscular blocking drug. In all groups, ventilation was controlled to maintain the end-tidal pCO_2 between 35 and 40 mmHg. Esophageal temperature was maintained between 35 and 36.5 °C by surface warming. The force of thumb adduction in response to supramaximal ulnar nerve stimulation, at a frequency of 2 Hz for 2 seconds repeated every 15 seconds, was monitored and recorded.

An iv bolus dose of doxacurium chloride that estimated its ED_{95}, 26 µg/kg in the N_2O/narcotic group or 15 µg/kg in the N_2O/inhaled anesthetic groups, was administered either 15 minutes after endotracheal intubation and/or after 15 minutes of a stable end-tidal isoflurane/halothane concentration. The onset time (time from injection to maximum effect), the maximum blockade developed, the time from injection to the beginning of spontaneous recovery of twitch tension and the clinical duration of action (time from injection to 25% recovery of control twitch tension) were measured. Control twitch tension was defined as the tension measurement taken prior to the administration of doxacurium chloride. All values were compared by Student's t-test. Differences were considered statistically significant when the p value was less than 0.05.

Results and Conclusions: The onset time, the maximum blockade developed and the clinical duration of action for a doxacurium chloride induced neuromuscular blockade did not differ significantly between the N_2O/narcotic, N_2O/isoflurane or N_2O/halothane groups. However, patients who received a N_2O/halothane anesthetic did demonstrate a shorter time to spontaneous recovery than did those who received either the N_2O/narcotic or N_2O/isoflurane anesthetic. Previous investigators have shown that isoflurane does augment the neuromuscular blockade produced by other long-acting nondepolarizing blocking agents (*d*-tubocurarine and pancuronium) to a greater extent than does halothane (3,4). We conclude that Doxacurium chloride is a potent nondepolarizing neuromuscular blocking agent that produces a similar neuromuscular blockade when administered at its ED_{95} dose to patients during a N_2O/narcotic and a N_2O/halothane anesthetic. In addition, its blockade appears to be augmented in patients receiving a N_2O/isoflurane anesthetic.

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Onset Time, Maximum Blockade, Spontaneous Recovery and Clinical Duration of Action for Doxacurium Chloride during Narcotic, Isoflurane or Halothane Anesthesia

	n^a	Narcotic	n	Isoflurane	n	Halothane
Onset Time	8	9.1 (2.4)	9	11.8 (3.4)	9	9.6 (1.5)
Maximum Blockade	8	94.1 (5.6)	9	88.0 (10.4)	9	84.8 (19.8)
Spon. Recovery	8	17.3 (6.0)	9	19.7 (5.8)	8^b	13.8 (1.9)*
Clinical Duration	8	52.9 (26.9)	8^c	49.7 (26.9)	8^b	40.3 (13.7)

Values (minutes) represent Mean (S.D.).

* $p<0.05$ Significant difference when compared to narcotic and isoflurane.

[a] One patient in the narcotic group was omitted due to the inadvertent administration of isoflurane during the induction of anesthesia.

[b] One patient in the halothane group was administered additional doxacurium chloride prior to the beginning of spontaneous recovery and could not be included in the calculation of either the spontaneous recovery time or the clinical duration of action.

[c] One patient in the isoflurane group only achieved 67% twitch depression following the initial dose of doxacurium chloride and could not be included in the calculation of the clinical duration of action.

Title: HIGH-DOSE SUFENTANIL ANESTHESIA: DRUG INTERACTIONS WITH PREMEDICATION AND NEUROMUSCULAR RELAXANTS

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Introduction The hemodynamic response to anesthetic induction with fentanyl is influenced by preanesthetic medication and neuromuscular relaxants (1,2). Therefore, we hypothesized that the hemodynamic response to sufentanil induction would be determined by a premedication-relaxant interaction. This experiment tested the hypothesis in a randomized, double-blind placebo-controlled fashion.

Methods With institutional approval and written informed consent, 45 patients with ejection fraction (EF) ≥ 0.40 scheduled for elective coronary revascularization were randomly assigned to 1 of 4 study groups, and received different premedication-neuromuscular relaxant combinations: morphine-scopolamine + pancuronium (SP), lorazepam + pancuronium (LP), morphine-scopolamine + vecuronium (SV), or lorazepam + vecuronium (LV). All patients received triazolam 0.004 mg/kg PO at HS on the preoperative night. Premedication was lorazepam 0.06 mg/kg PO 90 min preoperatively, or morphine 0.1 mg/kg and scopolamine 0.006 mg/kg IM 60 min preoperatively. Each patient received an appropriate PO or IM placebo. Antianginal medications were continued until the time of surgery. In the operating room, Holter monitor (DelMar Avionics) ECG leads II and CS_5 were attached and continuously recorded. Intravenous, arterial and thermodilution pulmonary arterial catheters were inserted. Two min prior to induction, pancuronium or vecuronium 0.01 mg/kg IV was given from a blinded syringe while patients breathed 100 % O_2. Sufentanil, 10 µg/kg IV over 5 min was then administered. Upon loss of consciousness, a bolus of pancuronium or vecuronium 0.09 mg/kg IV was given. Patients were then ventilated with 100 % O_2 and intubated after completion of sufentanil infusion. Vasoactive agents or volatile anesthetics were given at the discretion of the attending anesthetist. Complete hemodynamic profiles were compiled prior to induction, after sufentanil 10 µg/kg and 1 min after intubation. Holter ECG recordings were examined retrospectively and blindly for myocardial ischemia, defined as new ST-segment depression of ≥ 0.05 mV occurring 60 msec after the nadir of the S-wave. Compared to 0.10 mV, a diagnostic criterion of 0.05 mV increases the sensitivity but decreases the specificity of ECG detection of myocardial ischemia (3). Analysis of variance (ANOVA) was applied to demographic and hemodynamic data, and the Least Squares Means Test with Bonferroni's correction was used for multiple comparisons. Fischer's Exact Test or Chi-square analysis was used for contingency table analysis. A p-value of ≤ 0.05 was considered significant.

Results The groups did not differ in demographic characteristics or antianginal therapy. Premedication-relaxant combinations significantly influenced the hemodynamic response to induction. ANOVA revealed significant group-time interactions for heart rate (HR), mean arterial pressure (MAP) and pressure-rate ratio (PRR = MAP/HR) (4)(Fig). The SP combination caused tachycardia and decreased PRR. The LP combination did not cause tachycardia. Heart rate was stable with SV but declined after LV. MAP fell significantly with induction in both lorazepam groups. Four of 12 patients in group SP required IV propranolol during induction and intubation compared with none in the other groups (p=0.003). The incidence of new ST-segment depression of 0.05 mV was: SP 5/12, LP 2/10, SV 0/12, LV 0/11 (p=0.01, SP *vs* all others). Two of 12 patients in group SP developed new ST-segment depression of 0.10 mV, compared with none in the other groups (p=0.07).

Discussion The hemodynamic response to induction with sufentanil reflects a drug interaction involving preanesthetic medication and neuromuscular relaxants. The combination of scopolamine and pancuronium is particularly parasympatholytic, impairs myocardial oxygen balance, and increases the incidence of myocardial ischemia during induction. Conversely, the combination of lorazepam and vecuronium is not parasympatholytic, and therefore the vagotonic effect of sufentanil is apparent. The other combinations, SV and LP, lead to stable hemodynamics during induction. These findings are qualitatively similar to those of previous experiments with fentanyl. When considered with other important variables such as narcotic dose regimen, antianginal therapy, ventricular function, and IV sedative-hypnotic adjuncts, the concept of premedication-relaxant drug interactions can be used to predict the hemodynamic response to induction with narcotics.

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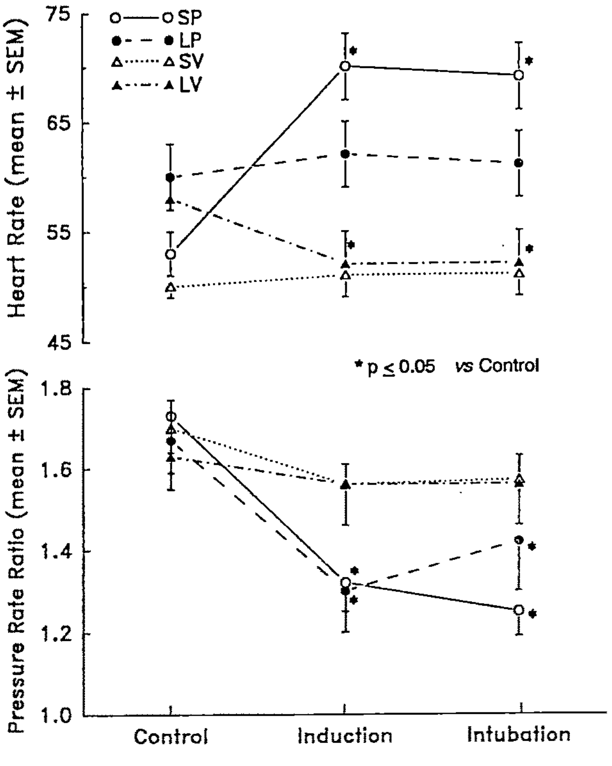

Title:

THE ATTENUATION OF THE STRESS RESPONSE WITH LOW DOSE SUFENTANIL DURING CEREBRAL ANEURYSM SURGERY.

Authors: B. Mahendran, M.B., B.S., P.H. Manninen, M.D., R.N. Merchant, M.D.
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Introduction. Anesthesia for cerebral aneurysm surgery requires cardiovascular stability, and rapid awakening postoperatively to permit neurological assessment of the patient. The aim of this study was to investigate the effects of low dose sufentanil anesthesia on the stress response to cerebral aneurysm surgery by the measurement of catecholamine and hemodynamic variables.

Methods. After institutional approval, informed consent was obtained from 20 patients presenting for clipping of cerebral aneurysms. Patients receiving beta blockers were excluded. Patients were unpremedicated. Following sedation with $1\mu g.kg^{-1}$ sufentanil and infiltration with local anesthesia, a radial artery catheter was inserted. Anesthesia was then induced in a standardized manner with lidocaine 1 $mg.kg^{-1}$and a titrated dose of thiopentone. Endotracheal intubation was facilitated by succinylcholine 1 $mg.kg^{-1}$ or vecuronium 0.1 $mg.kg^{-1}$. Anesthesia was maintained with O_2/air, isoflurane (0.5 -1%) and supplemental doses of sufentanil up to a total of $2\mu g.kg^{-1}$. Other monitors included electrocardiogram, end-tidal capnometer, central venous catheter and oral temperature probe. Five minutes prior to the insertion of head pins, sufentanil $0.2\mu g.kg^{-1}$ was administered and, where indicated, isoflurane was increased to 1%. Patients were mechanically ventilated to maintain $PaCO_2$ of 30-32 mmHg. All patients received 1-2 $g.kg^{-1}$ mannitol 20%. Isoflurane induced hypotension was used in six patients. Hemodynamic measurements included mean blood pressure (MBP) and heart rate (HR). Arterial blood was drawn for the measurement of catecholamines - epinephrine and norepinephrine. All measurements were taken at the following times: 1) Following sedation with sufentanil (control). 2) Three minutes after intubation. 3) Four minutes after insertion of head pins. 4) During stable anesthesia. Statistical analysis of data was performed using analysis of variance with repeated measures. $p<0.05$ was considered significant.

Results. Sixteen of the patients were female and 4 male; mean age (±SD) was 52 ± 11 yrs; mean weight was 75 ± 18 kg. The mean dose (±SD) of thiopentone required for induction of anesthesia was 4.2 ± 1.7 $mg.kg^{-1}$. Total mean dose of sufentanil used was 1.5 ± $0.3\mu g.kg^{-1}$. None of the patients required naloxone postoperatively. Surgical conditions, including brain relaxation, were excellent in all patients. Hemodynamic and plasma catecholamine values are shown in the table. There was no statistically significant increase in MBP or HR. One patient developed hypotension following induction of anesthesia, two showed hypertensive responses to intubation, and one to the insertion of head pins. There was no statistically significant increase in plasma catecholamines. Fifteen patients were fully alert and responsive within 20 minutes from the end of surgery. Five patients showed delayed awakening, one of whom had a poor neurological status pre-operatively and two had isoflurane induced hypotension intraoperatively.

Discussion. High dose sufentanil anesthesia has been shown to provide stress-free intraoperative conditions during neurosurgery, but may require reversal with naloxone [1,2]. In this study we have demonstrated that low dose sufentanil combined with minimal isoflurane anesthesia produces a stress-free intraoperative course, resulting in hemodynamic stability and attenuation of plasma catecholamine increases. This method also provided rapid awakening and extubation allowing early neurological assessment of the patient.

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TABLE
(Mean ±SEM)

	CONTROL	POST-INTUBATION	POST-P.N INSERTION	STABLE ANESTHESIA
Plasma Epinephrine	569±125	156±27*	130±27*	269±44*
Plasma Norepinephrine	2011±305	1837±193	1908±245	2033±237
MBP	84±3	71±4	67±3	73±2
HR	70±3	67±4	64±3	69±3

$p<0.05$ compared to control value

Title: ARE ALL PRETERM INFANTS LESS THAN 60 WEEKS POST-CONCEPTUAL AGE AT RISK FOR POSTOPERATIVE APNEA?

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Introduction: Preterm and ex-preterm infants are considered to be at risk for life-threatening apnea following general anesthesia. Although most accept that there is an increased risk of postoperative apnea in expreterm infants ≤ 44 weeks post-conceptual (P-C) age,[1,2] Kurth et al recently suggested that this limit should be extended to 60 weeks P-C age.[3] The purpose of this prospective study was to define the upper age limit for ex-preterm infants at risk of postoperative apnea and to identify any predisposing factors.

Methods: With approval from the Institutional Ethics Committee, all preterm infants < 37 weeks gestational age at birth and < 60 weeks P-C age at the time of surgery were enrolled in the study. All preterm infants who were scheduled electively for postoperative ventilation were excluded. The anesthetic management was selected by the attending staff. At the completion of surgery, the patients were extubated in the operating room. Cardiorespiratory monitoring was initiated in the postanesthetic recovery unit and continued for a minimum of 12 apnea-free hours. All infants were monitored with an Edentec 2000W apnea monitor. This monitor displays heart rate and respiratory rate and records events during an alarm. Apnea was defined as a respiratory pause ≥ 15 seconds. Bradycardia was defined according to Kurth et al.[3] All apneas and bradycardias and the intervention required were recorded by the attending nurse. Statistical significance ($p < 0.05$) was determined using chi-square analysis with the Yates correction for continuity.

Results: Fifty-eight infants underwent 65 operations (Tables 1 and 2). Anesthesia was induced intravenously and maintained with inhalational anesthetic agents in all patients. Non-depolarizing neuromuscular blocking drugs were used in 20/65 operations and included atracurium (10), pancuronium (4), d-tubocurare (3) and gallamine (3). All muscle relaxants were reversed at the completion of surgery. Narcotics were used in 3 patients.

Twenty-one infants were ≤ 42 weeks P-C age, 32 were between 43 and 51 weeks P-C age and 12 were > 51 weeks P-C age. Seven of the 21 infants < 42 weeks P-C age had postoperative apneas. The initial postoperative apneic episode in these infants occurred within 6 hours after surgery. Apneas continued for 4-48 hours after surgery. Breathing did not resume spontaneously in any of these 7 patients. Three patients required tactile stimulation while 4 required oxygen and continuous positive airway pressure by mask. Of these 7 patients, 4 had a history of apneas in the neonatal period.

Three infants in the 43-51 weeks P-C age group had episodes of bradycardia lasting 3-5 seconds. These episodes were not associated with apnea or color change and resolved spontaneously without intervention. None of the infants who were > 51 weeks P-C age had episodes of apnea or bradycardia postoperatively. Of the 10 patients who had operations on the central nervous system (myelomeningocele repair and ventriculoperitoneal shunt), 2 had postoperative apneic episodes.

Discussion: The overall incidence of apneas in this study (10.8%) is similar to that found by Liu et al[1] and Steward,[2] but less that that reported by Kurth et al (37%).[3] This discrepancy may be attributed to different patient populations and to the different anesthetic techniques used.

Our data indicate a significantly greater risk for postanesthetic apneas in ex-preterm infants ≤ 42 weeks P-C age. These infants should be monitored as inpatients until apnea-free for a minimum of 12 hours after surgery. The significance of the bradycardias which resolved without intervention in the patients between 43 and 51 weeks P-C age is unclear. It remains our practice to monitor these infants until further data are available. Infants > 51 weeks P-C age do not appear to be at risk for developing postanesthetic apneas.

Supported in part by Edentec, Eden Prairie, Minnesota.

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3. Kurth CD, Spitzer AR, Broennle AM, Downes JJ. Postoperative apnea in preterm infants. Anesthesiology 1987; 66:483

TABLE 1

PATIENT CHARACTERISTICS

Birth Weight (kg)	1.64 ± 0.63 (0.57 - 3.3)
Current Weight (kg)	4.35 ± 1.42 (1.38 - 7.4)
Gestational Age (wks)	31.4 ± 3.7 (24 - 36)
P-C Age (wks)	46.5 ± 6.1 (35 - 60)

Data are means ± SD (range)

TABLE 2

OPERATIONS	NUMBER OF PATIENTS
Herniorrhaphy	39
Pyloromyotomy	3
Laparotomy	4
Myelomeningocele Repair	1
Ventriculoperitoneal Shunt	9
Miscellaneous Minor Procedures	9

Title: BLOOD/GAS SOLUBILITY OF SEVOFLURANE, ISOFLURANE AND HALOTHANE IN PRETERM NEWBORNS, FULL-TERM NEWBORNS AND ADULTS

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Introduction: The more rapid rate of rise of alveolar anesthetic partial pressure in infants and children compared to adults may be explained in part, by the lower blood solubility of volatile anesthetics in infants and children.[1] This lower solubility may be attributed to the lower concentrations of proteins and lipids in infants and children than in adults.[1] Since the serum concentrations of proteins and lipids are lower in preterm newborns than in full-term newborns,[2] we undertook this study to compare the blood/gas partition coefficients of volatile anesthetics in preterm newborns to those in full-term newborns and adults.

Methods: Three groups of subjects were investigated: (1) 10 preterm newborns (mean gestational age 31.6 weeks), (2) 8 full-term newborns (mean gestational age 39 weeks), (3) 8 fasting adult volunteers (ASA physical status I or II). Fifteen ml of blood were collected from the umbilical vein of the placenta of each newborn at delivery and from a peripheral vein of each adult volunteer. Each blood sample was divided into 2 aliquots. Serum was separated from a 3 ml aliquot for determination of the serum concentrations of albumin, globulin, cholesterol and triglycerides. A 12 ml heparinized sample was used for determination of the blood/gas partition coefficients of sevoflurane, isoflurane and halothane. The blood/gas partition coefficients were determined at 37°C in triplicate using a method described previously.[3] Statistical significance ($p < 0.05$) was determined using analysis of variance and Student's t-test. Correlations between the blood/gas partition coefficients in preterm newborns and both gestational age and the concentrations of serum constituents were determined using multiple regression analysis.

Results: The blood/gas partition coefficients (mean ± SD) of sevoflurane, isoflurane and halothane did not differ significantly between preterm newborns and full-term newborns (Table). The blood/gas partition coefficients of isoflurane and halothane in preterm and full-term newborns were significantly lower than those in adults (Table) ($p < 0.05$). In contrast, the blood/gas partition coefficients of sevoflurane did not change significantly with age. We found no correlation between the blood/gas partition coefficients of the three volatile anesthetics and gestational age. The blood/gas partition coefficient of isoflurane correlated significantly with the serum concentration of triglycerides ($r^2 = 0.72$) ($p < 0.05$).

Discussion: The blood/gas partition coefficients of sevoflurane, isoflurane and halothane in full-term newborns and adults are in close agreement with those published previously.[1] Our results indicate that the blood/gas partition coefficients of sevoflurane, isoflurane and halothane do not change significantly with gestational age. Although the blood/gas partition coefficient of sevoflurane does not increase significantly from preterm newborns to adults, those of isoflurane and halothane do increase significantly with age ($p < 0.05$).

Acknowledgement: Sevoflurane was supplied by Maruishi Pharmaceutical Co. Ltd., Japan.

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TABLE

	Preterm Newborn	Full-term Newborn	Adult
Blood/gas Solubility:			
Sevoflurane	0.655 ±0.019	0.657 ±0.036	0.684 ±0.019
Isoflurane	1.226* ±0.058	1.251* ±0.069	1.375 ±0.057
Halothane	2.256* ±0.142	2.256* ±0.137	2.568 ±0.146
Serum Concentration:			
Albumin (gm/L)	32.32 ±6.96	27.5 ±7.43	41.38 ±4.47
Globulin (gm/L)	22.32 ±8.87	17.75 ±6.16	25.63 ±4.03
Cholesterol (mM)	2.48 ±0.68	1.66 ±0.35	4.11 ±0.62
Triglycerides (mM)	0.91 ±1.05	0.47 ±0.29	1.04 ±0.18

Data are mean (±SD) values
*$p < 0.05$ compared to adults

Title: EFFECT OF THE VOLUME OF 0.125% BUPIVACAINE ON THE EFFECTIVENESS OF CAUDAL ANALGESIA IN CHILDREN

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Introduction: Caudal blocks are widely used for postoperative analgesia after penoscrotal and inguinal surgery. Although the optimal concentration of bupivacaine with epinephrine for caudal analgesia has been investigated,[1] the optimal volume remains unclear. In this study we compared the effectiveness of 0.5 ml/kg and 1.0 ml/kg of 0.125% bupivacaine with 1:200,000 epinephrine for caudal analgesia in children following penoscrotal and inguinal surgery.

Methods: This prospective, randomized, double-blinded study was approved by the local institutional ethics committee. Informed, written consent was obtained from the parents of 80 children scheduled for hypospadias repair, non-plastibell type circumcision, inguinal hernia repair and orchidopexy. The patients were 1 to 10 years of age, ASA physical status I or II, fasting and unpremedicated. Anesthesia was induced with an intravenous technique and maintained with a volatile anesthetic with or without a muscle relaxant. Narcotics were not administered to these patients preoperatively or during surgery.

A caudal block was administered at the completion of surgery. Each patient was randomly assigned to receive either 0.5 ml/kg or 1.0 ml/kg of 0.125% bupivacaine with 1:200,000 epinephrine. After awakening from anesthesia the patient was transferred to the recovery room.

Postoperative pain and lower extremity motor function were evaluated at 1, 2, 4 and 12 hours by blinded observers. Pain was assessed using a scoring system described previously.[2] Motor strength was evaluated on a four point scale ranging from paralyzed (1) to forced movement against gravity (4).[1] Analgesic medications were administered according to the surgical standing orders at the discretion of the nurses if the pain score exceeded 3. The time intervals from caudal block to administration of supplemental analgesia and to first micturition during the 12 hour period following the caudal block were recorded.

Power analysis was performed prior to the study to indicate the minimum number of patients required in the study (total = 80). Statistical significance ($p < 0.05$) was determined using Chi-square analysis with the Yates correction for continuity for non-parametric data and Student's t-test for parametric data.

Results: Of the 80 patients, 40 received 0.5 ml/kg and 40 received 1.0 ml/kg of 0.125% bupivacaine with 1:200,000 epinephrine. The mean age, weight and type of surgery did not differ significantly between the two groups (Table). One patient in the 0.5 ml/kg group was excluded from the analysis because he required a second surgical procedure within 6 hours of the caudal block. Supplemental analgesic requirements did not differ significantly between the 2 groups at any time during the first 12 hours after the block (Figure). The adequacy of caudal analgesia, i.e. pain score < 3 and no codeine required, did not differ significantly between the 2 groups. Thirty-seven of the 39 patients in the 0.5 ml/kg group and 31 of the 40 patients in the 1.0 ml/kg group were able to stand with minimal assistance 1 hour after the block (p = NS). No patient had detectable weakness 12 hours after the block.

Discussion: The preliminary results of this study indicate that both 0.5 and 1.0 ml/kg of 0.125% bupivacaine with 1:200,000 epinephrine provide adequate postoperative analgesia with minimal side effects in children undergoing both penoscrotal and inguinal surgery.

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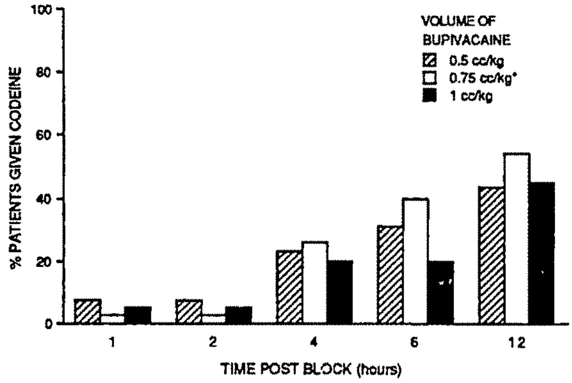
TABLE

	VOLUME OF BUPIVACAINE*	
	0.5 ml/kg	1.0 ml/kg
Age (yrs)	3.69 ± 1.94	3.91 ± 1.89
Weight (kg)	16.7 ± 4.7	16.2 ± 4.1
Number of Procedures:		
Orchidopexy/Hernia Repair	13	12
Hypospadias/Circumcision	27	28

Data are mean ± SD
*0.125% bupivacaine with 1:200,000 epinephrine

FIGURE



*Wolf et al, Anesthesiology, 1988

Title: THE EFFECT OF SUCCINYLCHOLINE ON SERUM POTASSIUM IN PATIENTS WITH ACUTELY RUPTURED CEREBRAL ANEURYSMS

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Introduction. Succinylcholine-induced hyperkalemia may occur in patients with neurological disorders including patients late after a subarachnoid hemorrhage (SAH) from a ruptured cerebral aneurysm.[1,2] Recent neurosurgical practice is to operate on patients early following a SAH. The purpose of this study was to assess the effect of succinylcholine on serum potassium (K^+) in patients undergoing early (less than 4 days) surgical treatment of their ruptured cerebral aneurysm.

Method. After institutional approval, informed consent was obtained from 30 patients undergoing cerebral aneurysm surgery. Patients were classified according to the number of days from SAH to surgery (Table). Patients were unpremedicated. An intra-arterial catheter was inserted under local anesthesia. Anesthesia was induced with fentanyl 3-5 μg.kg^{-1} (n = 24), or sufentanil 0.5 - 1.0 μg.kg^{-1} (n = 6), sodium thiopentone 5-6 mg.kg.$^{-1}$ and lidocaine 1 mg.kg.$^{-1}$. Succinylcholine 1 mg.kg.$^{-1}$ was then administered. Eleven patients received d-tubocurare (3 mg) prior to succinylcholine 2 mg.kg.$^{-1}$. Anesthesia was maintained with air/oxygen and isoflurane. The patients were ventilated to a $PaCo_2$ of 32-35 mg Hg. Blood for serum K^+ was obtained from the arterial catheter at the following times: I) Prior to induction, II) Following administration of succinylcholine at 1 min, III) 5 min, and IV) 10 min. Arterial blood gases were measured at times I and IV. Lead II electrocardiogram was monitored continuously. Statistical analysis was performed using analysis of variance. $P < 0.05$ was considered significant.

Results. No anesthetic related complications occurred. Seventeen females and 13 males were studied, mean age (±SD) was 52 ± 12 years, and mean weight 70 ± 13 kg. There was no statistically significant increase in serum K^+ at any time (Table). The highest rise in serum K^+ in any individual patient was 0.9 mmol.$^{-1}$ at 1 min. Measurements of pH and $PaCO_2$ were not significantly different between the groups. No statistically significant difference was associated with the use of d-tubocurare. Five patients had a neurological deficit (hemiparesis) preoperatively. The changes in K^+ of this group were not statistically different from patients with no deficits.

Discussion. We were unable to demonstrate the magnitude of hyperkalemic changes found by Iwatsuk.[2] They found that the patients at risk were those who had surgery 10 - 50 days following SAH, but were unable to explain the hyperkalemia on the basis of hyper-sensitization of skeletal-muscle by denervation or by muscle atrophy. In our study the presence of neurological deficits did not result in hyperkalemia, though only 2 of our patients with neurological deficits were more than 10 days from their SAH. We conclude that patients undergoing early surgery following SAH are not at increased risk for development of succinylcholine-induced hyperkalemia.

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TABLE

DAYS FROM SAH	SERUM K^+ (mmol.$^{-1}$ AT TIMES OF SAMPLING				MAXIMUM MEAN CHANGE IN K^+
	I	II	III	IV	
< 2 n = 4	3.9±.39	3.8±.36	4.0±.59	4.0±.42	.4±.17
3 - 4 n = 6	3.6±.44	3.6±.44	3.7±.51	3.9±.54	.4±.17
5 - 9 n = 5	3.5±.19	3.7±.31	3.7±.4	3.7±.31	.24±.21
10 - 15 n = 9	4.0±.31	4.1±.45	4.3±.46	4.4±.47	.54±.23
>16 n = 6	4.0±.26	4.2±.58	4.3±.35	4.4±.42	.45±.27

n = number of patients
values are mean±SD

Title: CALCIUM BLUNTS EPINEPHRINE'S CARDIAC, PERIPHERAL VASCULAR, AND HYPERGLYCEMIC EFFECTS IN POST-OPERATIVE HEART SURGERY PATIENTS

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Introduction. Clinicians use both calcium (Ca) and epinephrine to resuscitate patients with depressed cardiovascular function. Since epinephrine's effects are mediated through an elevation of free intracellular Ca ions, many clinicians administer Ca with epinephrine, hoping to augment epinephrine's effects.(1) This study tests whether co-administration of Ca with epinephrine improves epinephrine's efficacy in patients recovering from open heart surgery.

Methods. Following approval of our protocol by the Institutional Review Board, 12 consenting patients recovering from open heart surgery first received either Ca chloride (2.5 mg/kg elemental Ca bolus followed by an infusion of 0.5 mg/kg/hr elemental Ca) or 5% dextrose (D5W; bolus and infusion) in a randomized, double-blinded fashion. Twenty minutes later, all patients received 2 incremental infusions of epinephrine [0.01 (LEPI) and 0.03 (HEPI) μg/kg/min], each for 8 minutes. A 15-min rest period followed, which allowed for dissipation of epinephrine's effects. Then the experimental sequence was repeated, except that those first given Ca now received D5W, and those initially given D5W now received Ca. Plasma ionized Ca, K, epinephrine and glucose; central venous, arterial, and pulmonary arterial pressures; and duplicate thermodilution cardiac outputs were recorded at baseline (D5W-0 or Ca-0), 20 min into the Ca (Ca-20) or D5W infusion (D5W-20), and at steady-state during the sequential administration of the two epinephrine infusions (LEPI and HEPI). Each patient served as his own control. Data are presented as mean ± SE. Significance of results was determined using analysis of variance for repeated measures followed by t-test with Bonferroni's correction.

Results. Table 1 illustrates the effects of the two doses of epinephrine on mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance index (SVRI), ionized Ca, and glucose in the presence and in the absence of the Ca infusion. Calcium blunted epinephrine's cardiovascular and hyperglycemic effects at both epinephrine doses. Neither calcium nor epinephrine had significant effects upon CVP, PCWP, PAP, HR, and K concentration. The plasma concentrations of epinephrine achieved with the epinephrine infusions were similar in the presence of D5W or calcium.

Discussion. Calcium blunted epinephrine's effects at the cardiac β_1 receptor (CI), peripheral vascular β_2 receptors (SVRI), and hyperglycemic β_2 receptors (glucose). Although Ca interacts with a variety of hormones and neurotransmitters, interaction between Ca and β-receptors has not been previously reported. Our epinephrine findings in humans are consistent with attenuation by Ca of norepinephrine and epinephrine-induced peripheral vasoconstriction in animals (2,3), and with Ca-mediated activation of cAMP-phosphodiesterase in cardiac tissue.(2)

Ca, once used routinely following cardiopulmonary bypass, is now used more sparingly since it may cause systemic and coronary artery vasoconstriction, increased myocardial oxygen consumption, and ischemic cell injury.(4-7) Although Ca still has a role in the treatment of decreased contractility of short duration, especially following a hyperkalemic insult, the potential dangers of Ca administration must be considered. We conclude that routine Ca administration to normocalemic patients is ill-advised, whether following cardiopulmonary bypass or cardiac arrest, especially if the patients are to receive epinephrine or other similarly acting inotropic agents.

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TABLE 1: EFFECTS OF EPINEPHRINE DURING CALCIUM OR DEXTROSE INFUSIONS (N=12)

GROUP	CI (L/min/m^2)	MAP (mmHg)	SVRI
D5W-0	2.8 ± 0.2	86 ± 2	2343 ± 179
D5W-20	2.7 ± 0.2	86 ± 2	2453 ± 185
LEPI	3.0 ± 0.2*	87 ± 2	2209 ± 197
HEPI	3.6 ± 0.3*	95 ± 2	2023 ± 194*
Ca-0	2.9 ± 0.2	85 ± 2	2166 ± 200
Ca-20	2.9 ± 0.2	92 ± 2*	2408 ± 192
LEPI-Ca	2.9 ± 0.2	91 ± 2	2413 ± 243
HEPI-Ca	3.2 ± 0.2	93 ± 2	2250 ± 206

	Ca^{++} (mM)	GLUCOSE (mg/dl)
D5W-0	1.12 ± .03	202 ± 19
D5W-20	1.13 ± .03	207 ± 20
LEPI	1.11 ± .03	222 ± 21
HEPI	1.12 ± .03	265 ± 22^{+}
Ca-0	1.06 ± .03	174 ± 16
Ca-20	1.30 ± .04*	205 ± 13
LEPI-Ca	1.23 ± .03*	212 ± 11
HEPI-Ca	1.22 ± .03*	233 ± 14

All data expressed as means ± standard errors.
* $p < 0.05$

Title: LOCAL ANESTHESIA OF THE BRAIN: LIDOCAINE RENDERS RAT HIPPOCAMPAL NEURONS HYPERPOLARIZED AND HYPOEXCITABLE MUCH LIKE CONVENTIONAL GENERAL ANESTHETICS

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Introduction. Although the exact mechanism by which general anesthesia is produced has yet to be identified, most general anesthetics share a number of electropharmacological actions, including dose-dependent elevation of firing threshold and membrane hyperpolarization (1,2). Local anesthetics, which produce regional anesthesia by inhibiting sodium channel function in peripheral nerve axons, will also produce general anesthesia when administered intravenously. To explain this phenomenon, we applied lidocaine to rat pyramidal cells to determine whether lidocaine's actions on central neurons resemble those of general anesthetics.

Methods. Male Sprague-Dawley rats 175 to 199 grams were decapitated and their brains placed in cold, oxygenated artificial cerebrospinal fluid (ACSF). Hippocampi were sliced with a Stoelting tissue chopper into 400 micron sections and placed in a linear flow recording chamber. Tissue was supported with oxygenated ACSF at 34 to 36°C. Afferent inputs to the CA1 pyramidal cells were activated with 0.1 msec pulses through a bipolar stimulating electrode placed in the Schaffer collaterals of the stratum radiatum. Intracellular recordings from CA1 pyramidal cells were obtained using a 4M K-acetate microelectrode. Intracellular current pulses were administered with the Dagan 8100-1. Data were stored on magnetic tape and analyzed off-line.

Results. Studies were performed on pyramidal cells obtained from 12 animals. Baseline data were compared with data collected following application of lidocaine. Figure 1 illustrates the change in threshold for eliciting three spikes. Lower concentrations of lidocaine (50 µM followed by 100 µM) (A) exhibited changes in threshold after a greater length of time than higher concentrations (500 µM) (B). Table 1 gives data collected for 500 µM lidocaine. Lidocaine significantly increased the threshold for a current single spike. The membrane hyperpolarization (at this dose) was of borderline ($p \approx 0.06$) significance. Thus, lidocaine reversibly increased threshold and hyperpolarized neurons at concentrations which had negligible effects on spike amplitude.

Discussion. Lidocaine had effects upon pyramidal cells similar to those of other, more conventional, general anesthetics agents. Low concentrations of lidocaine hyperpolarized neurons comparably to anesthetic concentrations of halothane and ether (2). In common with halothane, hyperpolarization and increases in firing threshold were induced by drug concentrations below those required to significantly reduce sodium currents in either central or peripheral neurons (1,2,3). These findings support our hypothesis that lidocaine general anesthesia results from membrane potential and threshold changes rather than from absolute impulse blockade.

This research was supported in part by a B. B. Sankey Anesthesia Advancement award.

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FIGURE 1:

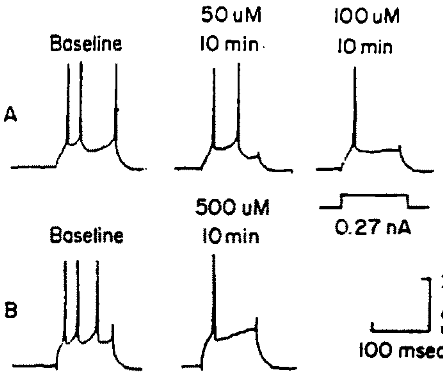

TABLE 1:

	Threshold (NA)	Resting Potential (-mV)	Spike Amplitude (mV)
Baseline	.2906 ± .1835	-64.72 ± 8.25	101.13 ± 6.98
Lidocaine 500 µM	.4097 ± .2291*	-65.66 ± 8.90	99.13 ± 9.71

All data expressed as mean ± standard deviations

* $P < 0.001$

Title: PROTECTIVE EFFECT OF ENFLURANE BUT NOT ISOFLURANE AGAINST HYPOXIC INJURY IN THE ISOLATED GUINEA PIG HEART.

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Introduction. Volatile anesthetics have generated recent interest as agents which may reduce myocardial damage during ischemia and during reperfusion (1,2). In nonischemic tissue, halothane has been shown to depress contractility and the rise in free intracellular calcium concentration during contraction (3). In ischemic regions of the isolated heart, halothane depresses tissue calcium overload (2). In addition, halothane significantly improves functional recovery of isolated hearts from a global hypoxia (4). The present study examines the direct effects of isoflurane and enflurane on functional recovery of the myocardium following global hypoxia in the isolated guinea pig heart.

Methods. Thirty-one guinea pigs (350-500 g) were decapitated after I.P. administration of ketamine (20 mg) and haparin (1000 units). The hearts were quickly excised and perfused at constant pressure (55 mmHg) by the Langendorff technique with modified Krebs-Ringer solution equilibrated with 97% O_2 and 3% CO_2 (pH 7.38 and PO_2 500 mmHg) at 36.5°C. Heart rate (HR) and atrioventricular conduction (AV) time were recorded with bipolar electrodes placed in the right atrium and right ventricle for on-line analysis. Left ventricular (LV) systolic and diastolic pressure were measured with a transducer connected to a thin latex balloon inserted into the left ventricle through the mitral valve. Balloon volume was initially adjusted to zero diastolic pressure. Isoflurane and enflurane at 1.5% and 2.25% were delivered by vaporizers and measured at the aorta by gas chromatography (mean 0.49 and 0.85 mM, respectively). After a 30 min equilibration period, all hearts were perfused for 30 min with a solution equilibrated with 97% N_2 and 3% CO_2 (PO_2 90 mmHg) followed by 40 min of reoxygenation. In the anesthetic group, agents were present for 10 min prior, during and for 10 min after the hypoxic period. Measurements were made at initial control, after 10 min anesthetic, at 5, 15 and 30 min of hypoxia and at 10 and 40 min of reoxygenation. Statistical differences were determined by using Students t-test and analysis of variance.

Results. Isoflurane and enflurane decreased heart rate by 11 and 14% and increased AV time from 61 to 75 and 68 to 91 ms, respectively. During reoxygenation HR and AV conduction recovered completely to initial control levels in all three groups. Effects of these agents and hypoxia on LV systolic and diastolic pressures are shown in Figure 1 & 2, respectively. Although enflurane produced a greater decrease in systolic pressure during the hypoxia and initial reoxygenation, final recovery was significantly greater as compared to the control and the isoflurane group. Diastolic pressure remained elevated after reoxygenation in the control and isoflurane group, while it returned to its control level in the enflurane group. The incidence of ventricular fibrillation (VF) in control, isoflurane and enflurane groups was 44, 31 and 11%, respectively.

Discussion. The volatile anesthetics are known to directly depress cardiac pacemaker activity, conduction times, contractility and coronary vascular tone. These agents may act at multiple sites to depress the calcium inward current, to interfere with the calcium sensitivity of myofibrillar proteins to calcium, and release of calcium by the sarcoplasmic reticulum. This study indicates that the presence of enflurane significantly improves functional recovery of isolated hearts from a hypoxic episode as assessed by: a) lower diastolic pressure; b) improved myocardial contractility; and c) lower incidence of VF. In the presence of isoflurane the drop in systolic pressure was smaller as compared to the enflurane group, but the recovery was the same as the control group. We attribute the lack of protection from hypoxia in the isoflurane group to a smaller depression in intracellular calcium (5). Thus, it seems likely that enflurane and halothane (4) may reduce the extent of myocardial damage and the incidence of VF during ischemia and improve functional recovery on reperfusion.

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Fig. 1

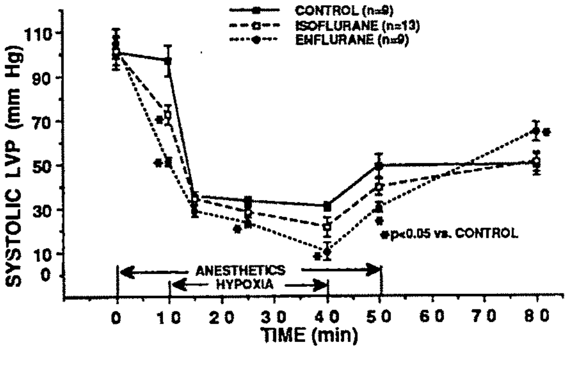
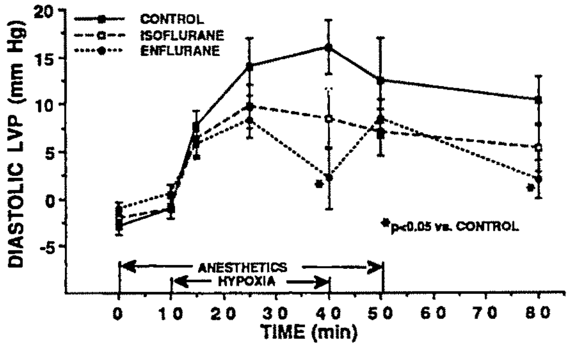


Fig. 2



TITLE: PENTOBARBITAL AND THE HYPOXIC PULMONARY VASOCONSTRICTOR RESPONSE

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Introduction: Hypoxic pulmonary vasoconstriction (HPV) is an homeostatic mechanism by which systemic arterial PO_2 is maintained. In the in vitro lung model, it has been reported that the injectable anesthetic, pentobarbital, inhibit this response[1]. This inhibition is not seen in vivo, and the present study has investigated the nature of this difference. A new animal model was developed in which an intact animal was used to process the perfusate to the isolated lung[2].

Method: Twelve adult female rabbits were anesthetized and maintained with ketamine and xylazine. A tracheotomy was performed and cannulae were placed in the femoral vein, femoral artery and carotid artery. Blood was circulated from the carotid artery to a reservoir and back to the femoral vein at a controlled rate. The isolated lung from a second group of animals was perfused from the reservoir in a second circuit and ventilated with normoxic (21% oxygen, 5% carbon dioxide) or hypoxic (3% oxygen, 5% carbon dioxide) gas mixtures, alternating for 6 minute challenges. The 12 animals and lungs were divided into two groups. Group A had 50 mg pentobarbital injected into the whole animal. In Group B, the processing of perfusate by the whole animal was discontinued and 50 mg pentobarbital was placed in the reservoir perfusing only the isolated lung. The dose of sodium pentobarbital was obtained from a dose/response curve in which 12 isolated rabbit lungs were randomly divided into two groups (Group C and Group D). The stabilization period and preliminary hypoxic challenges were the same for both groups and, after the fourth hypoxic challenge, the drug or solvent (40% glycol, 10% alcohol and water) was added to the reservoir. This was followed by a 6 minute hypoxic challenge. This was repeated three times with increasing and accumulating concentrations of the drug (100 µg, 1 mg, 10 mg, 40 mg/60 mls perfusate) or solvent (0.5 ml/60 mls perfusate).

Results: The dose/response curve for the isolated lung is shown in Figure 1 and indicates that the response to hypoxia was completely inhibited at 50 mg sodium pentobarbital/60 mls perfusate. The solvent had no appreciable affect on the hypoxic challenges. The results when 50 mg were given to the whole animal and/or isolated lung are shown in Table 1. When the whole animal processed the blood, there was no significant difference in the response to hypoxia (Group A). When pentobarbital was given directly to the lung (Group B), the response was significantly decreased (7.6 ± 1.0 to 1.4 ± 0.3).

Discussion: When 50 mg of pentobarbital is injected into the 60 ml fluid volume of the isolated lung circuit, the resulting perfusate concentration is approximately 3400 µM, which inhibited the response by 83%. In contrast, that same 50 mg dose injected into the intact animal would be expected to be clinically effective with a plasma concentration in the range of 40-80 µM[3]. This concentration did not and is not expected to inhibit HPV. It, therefore, appears that reports of inhibition of HPV by pentobarbital[1] may have been associated with concentrations in the toxic range.

TABLE 1
Pulmonary Artery Pressor Response
to 3% Hypoxic Gas Mixture (cm H_2O ± SE)

	Control	with Pentobarbital	
Group A	7.2 ± 0.4	7.8 ± 0.6	8.3 ± 0.8
Group B	7.6 ± 1.0	1.3 ± 0.3	1.4 ± 0.3

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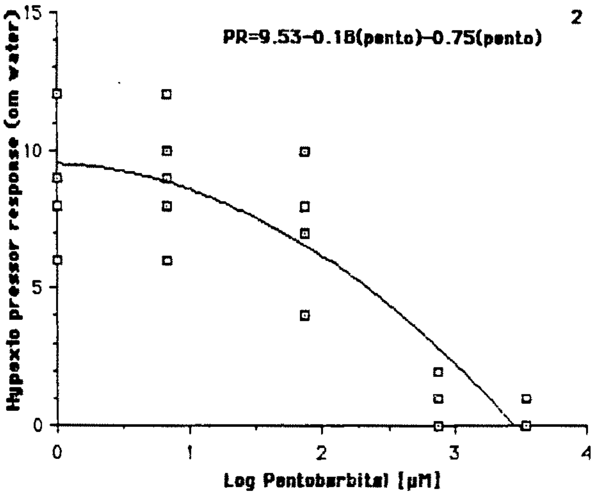
Supported in part by NIH GM29628.

FIGURE 1
DOSE RESPONSE CURVE FOR PENTOBARBITAL



Title: THE EFFECTS OF ANESTHETIC COMPOUNDS ON UPTAKE OF 5-HYDROXYTRYPTAMINE IN RAT BRAIN SYNAPTOSOMES

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Introduction: 5-hydroxytryptamine (5-HT; serotonin) is a neuroregulatory amine that is proposed to modulate sympathetic nervous system activity, body temperature, and pain perception (1-3). Central serotonergic activity has been shown to be essential for the MAC reduction of halothane by the opioid sufentanil (4). The administration of several anesthetic compounds results in alteration of brain 5-HT content (5). The current experiments were performed in order to identify a potential molecular mechanism involved in anesthetic-induced alterations of central 5-HT activity. Accordingly, the effects of halothane, ketamine, and sufentanil on 5-HT uptake in rat brain synaptosomes were investigated.

Methods: Following institutional animal use and care committee approval, male Sprague-Dawley rats were decapitated and brains removed. Synaptosomes were prepared by homogenization and differential centrifugation and 5-HT uptake assays carried out in Tris-Krebs buffer using [1,2 ^{3}H]5-HT (0.00156-0.2 uM) as substrate. Assays were performed in the presence (experimental) and absence (control) of the anesthetic drugs. Reactions were terminated by dilution with ice-cold buffer and synaptosomes collected by vacuum filtration. Radioactivity was measured by liquid scintillation counting. Statistical differences between means within groups were determined by analysis of variance followed by Dunnett's test. Significance was set at $p < 0.05$.

Results: At clinically relevant concentrations, halothane and ketamine inhibited synaptosomal accumulation of the amine in what appeared to a be a concentration-dependent manner. Sufentanil failed to alter 5-HT uptake at concentrations of up to 2.5 uM. The application of Michaelis Menten kinetic principles indicated both halothane and ketamine to be competitive with 5-HT for the uptake mechanism.

Discussion: The rate-limiting step in the termination of synaptic 5-HT is reuptake of the amine by a presynaptic neurolemmal Na^+-dependent transport mechanism. Acute inhibition at this step by anesthetic drugs would lead to increased exposure of 5-HT to post synaptic receptor sites. Pharmacologic manipulations leading to increased synaptic activity of 5-HT are associated with elevation of the threshold to nociceptive stimuli (3). Thus the observed results could represent a mechanism contributing to the analgesia of halothane and ketamine. The failure of sufentanil to alter uptake of the amine fails to support uptake inhibition as the mechanism responsible for MAC reduction of halothane described earlier (4).

Increased central 5-HT neurotransmission results in diminished sympathetic tone (1). Inhibition of 5-HT uptake by anesthetic compounds could contribute to alterations in cardiovascular function observed during the clinical use of these drugs.

It is appreciated that anesthetic agents interact with several neurotransmitter systems which themselves have complex relationships. It is therefore simplistic to infer that an effect by anesthetic compounds on a single neurotransmitter system has a cause and effect relationship. The current results do however provide important implications concerning the central activity of 5-HT and mechanisms of anesthetic action.

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THE EFFECTS OF ANESTHETIC COMPOUNDS ON

5-HT UPTAKE IN RAT BRAIN SYNAPTOSOMES

ANESTHETIC DRUG	5-HT UPTAKE $^+$ (per cent control)	TYPE OF INHIBITION
HALOTHANE		competitive
2 mM	36 ± 3 *	
4 mM	22 ± 3 *	
KETAMINE		competitive
10 µM	59 ± 7 *	
40 µM	23 ± 5 *	
SUFENTANIL 0.001-2.5 µM	No effect	-----------

Data are expressed as means ± S.E.M. where N = 4. * = p<0.01 versus control.

Title: INCIDENCE OF ETIOLOGY AND REINTUBATION IN THE POST-ANESTHESIA CARE UNIT: PHYSICIAN ERROR OR PATIENT DISEASE?

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Introduction. Inadequate airway management is a major factor in perioperative morbidity. Residual anesthetic effects and anatomic distortion secondary to surgery, as well as exacerbations of a patient's underlying illnesses, can all affect the management of a patient's airway in the Post-Anesthesia Care Unit (PACU). Ventilatory impairment so severe as to require reintubation of the trachea is clearly a life threatening complication. Therefore, we retrospectively reviewed all admissions (N = 11,620 patients) to our PACU for a period of 21 months from October 1986 through June 1988 to determine the incidence and etiology of all the reintubations occurring in the immediate recovery period.

Methods. Following Human Investigation Committee approval, we analyzed our computerized database which contains data from every patient admitted to our PACU.[1] The data sheets were completed on the day of admission, and contained extensive information on the patient's course in the PACU. For all patients identified as having been reintubated in the PACU, the complete hospital chart and detailed anesthesia and recovery records were reviewed for information concerning past medical history, surgical procedure, medications, anesthetic technique, fluid balance, ECG, lab values, and members of the surgical and anesthesia care team. We reviewed the notes of the physicians at the time of the reintubation, as well as incident reports that may have been filed but were not part of the formal hospital record. Statistical analysis was performed using Chi square and Poisson distribution with $p < 0.05$ considered significant.

Results. Of the 11,620 admissions to the PACU, airway support (oral or nasal airways or manual chin lift) was necessary in 8% (954) of patients. Twenty two patients (0.19%) required the insertion of an endotracheal tube while in the PACU. (Table) Of the 22 reintubations, 14 were directly related to anesthetic management. The seven (N=7) ENT cases were 0.6% of the total of 1151 ENT cases admitted to the PACU unit in the period reviewed. Of these seven cases, 2 were patients with bleeding at the operative site, 4 were examples of post-operative laryngeal edema, and one was a case of airway obstruction secondary to a goiter. There was no correlation between the occurrence of these cases and time of year, particular anesthesiologist or surgeon, specific anesthetic agent, or use of specific premedications (p = NS).

Discussion. The incidence of reintubation in this large series (0.19%) is similar to that in other reports.[2] Although the patients requiring reintubation in the PACU are a very small fraction of the total number of patients admitted, we believe that they demonstrate examples of error in judgement by the anesthesiologists or surgeons involved. It is clear that the 8 patients with persistent sedative or muscle relaxant effect are examples of error in management by the anesthesia care team. The patients with pulmonary edema must also be regarded as having excessive fluid replacement along with an erroneous estimation of cardiac reserve or coexisting illness. The patient with an unappreciated goiter and the patient in whom post-operative laryngeal edema should have been anticipated along with the 2 patients with bleeding at the operative site reflect errors in management as well. Thus, despite the low incidence of reintubation in a heterogeneous group of patients admitted to the PACU, preventable anesthesia and surgical complications accounted for 73% (16/22) of the reintubations.

TABLE
Reintubation in the PACU
N=11,620 patients;
Reintubation rate = 0.19%

A.	Airway obstruction related to head and neck pathology	7
B.	Excessive sedative or anesthetic drug effect	5
C.	Cardiogenic pulmonary edema	4
D.	Persistent muscle relaxant effect	3
E.	Miscellaneous (sepsis, transfusion reaction, psychogenic)	3
		22

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Title: PRE-OPERATIVE INDICES TO ANTICIPATE DIFFICULT TRACHEAL INTUBATION

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Introduction. Patients with obvious signs of probable airway problems (i.e. short neck, obesity, protruding incisors, high arched palate, etc.) are usually treated with additional caution. However, some patients who appear normal to conventional examinations may still present an unanticipated airway problem to the anesthesiologist. Previous studies have shown the visibility of oropharynx as the reliable criterion for prediction of intubation difficulty. We therefore studied the correlation between other criteria such as the distance from the thyroid notch to the mentum and the distance from the angle of mandible to the mentum with the oropharyngeal visibility classification.

Methods. After institutional approval, 44 adult patients (ASA Class I to II), scheduled for surgical procedures requiring intubation, were included in this study. Group A included 22 patients, 12 females and 10 males (ages 17-67 years). These patients had intubation difficulties that were not anticipated in the preoperative examination. Group B (control group) consisted of 22 patients, 12 females and 10 males (ages 16-58 years) whose intubations were performed at the first attempt without any difficulty whatsoever. The parameters studied were: (1) The thyromental distance which is the distance from the thyroid notch to the mental prominence when the neck is fully extended. (2) The horizontal length of the mandible, which is the distance from the angle of the mandible to the symphysis menti. These measurements were made in centimeters using a rigid ruler. (3) In addition, the oropharyngeal classification was done according to a previously described method (1) as follows:

Class I	- Where soft palate, fauces, uvula and pillars are visible.
Class II	- Where soft palate, fauces, and uvula are visible.
Class III	- Only soft palate and base of uvula are visible.
Class IV	- Soft palate not visible at all.

Radiological examination of the neck was also performed in all patients to rule out anatomical airway abnormalities.

Results. In Group A, the mean thyromental distance was 5.6 cms (S.D.±0.87). The mean horizontal length of the mandible was 8.5 cms (S.D.±0.54). Nine patients had Class IV pharynx and 13 patients had Class III pharynx. In Group B, the mean thyromental distance was 8.0 cms (S.D.±0.56). The mean horizontal length of the mandible was 10.8 cms (S.D.±0.75). Fourteen patients had Class I and 8 patients had Class II pharynx. Data analysis was performed using the Student T-test and the difference between the two groups was found to be statistically significant (p value <0.01). The results of our study are illustrated in Figure 1.

Discussion. This study demonstrated that patients with a thyromental distance < 6 cms and a horizontal length of the mandible < 9 cms showed a good correlation with Class III and IV pharynx, and had a higher probability of difficult intubation. On the other hand, those with distances of > 6 cms and > 9 cms respectively correlated well with a Class I and Class II pharynx, with a lower possibility of intubation difficulty. In conclusion, difficult intubations may be anticipated by careful preoperative assessment of all the above-mentioned criteria.

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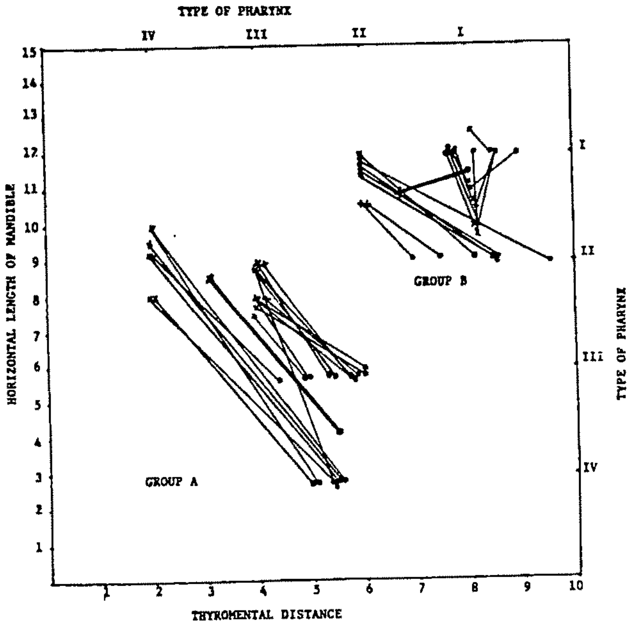
FIGURE 1



Title: EFFECTS OF ISOFLURANE ON HEPATIC CIRCULATION AND OXYGEN METABOLISM IN DOGS UNDER HYPOXIA

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Introduction. Isoflurane anesthesia maintains hepatic arterial and portal venous blood flows better, and hepatic oxygen supply-demand ratio higher than halothane anesthesia in the normoxic condition. However, hepatic necrosis and death following isoflurane anesthesia was recently reported (1). The mechanism of anesthesia-induced hepatotoxicity is not known at the present time. Although anaerobic metabolism of anesthetics, especially in the case of halothane anesthesia, has been suspected of producing hepatotoxicity, hepatic hypoxia brought on by respiratory and/or circulatory depression during anesthesia could be the main cause of anesthesia-induced hepatotoxicity (2). The present study was designed to determine whether isoflurane would reduce hepatic circulation and hepatic oxygen metabolism in the presence of hypoxia, unlikely as in the normoxic condition.

Methods. Twenty-two mongrel dogs were studied. Anesthesia was induced with ketamine (50mg i.m.) and thiopental (10-20mg/kg i.v.). Under the control ventilation with pancuronium, the animals were anesthetized with N_2O-O_2 (FiO_2 0.5). Following laparotomy, hepatic arterial blood flow (HABF) and portal venous blood flow (PVBF) were measured with electromagnetic flowmetry, and cardiac output (CO) was measured by thermodilution as baseline values for control. Hepatic oxygen supply ($\dot{D}hepO_2$) and consumption ($\dot{V}hepO_2$) were calculated by multiplying blood flows of the hepatic artery and portal vein by oxygen contents in the arterial, portal venous and hepatic venous blood. Thereafter, ten dogs were anesthetized with halothane (N_2O-O_2-halothane 1.8%) and 12 dogs with isoflurane (N_2O-O_2-isoflurane 2.7%) in the presence of hypoxia (FiO_2 0.14). At the end of an hour-long anesthesia, measurements described above were repeated, and then again two and four hours after anesthesia with the animals in the room air. Serum hepatic enzymes (LDH, GOT, and GPT) were measured before laparotomy, before anesthesia and four hours after anesthesia. $PaCO_2$ and the body temperature were maintained within normal ranges. Paired and unpaired t test were used for statistics, and differences were declared significant with $p < 0.05$.

Results. Mean arterial pressure (MAP), CO, HABF, PVBF, total hepatic blood flow (THBF), $\dot{D}hepO_2$, $\dot{V}hepO_2$, hepatic venous oxygen content ($ChvO_2$), LDH, GOT and GPT were not significantly different between the halothane and isoflurane groups before exposure to each anesthetic. MAP decreased to approximately 70mmHg in both anesthesia groups during anesthesia and there was no significant difference between the groups. While CO decreased to 60.5% of baseline value during halothane anesthesia, it did not significantly decrease during isoflurane anesthesia. HABF, PVBF and THBF significantly decreased to 58.2, 48.5 and 51.0% of control values respectively during halothane anesthesia. HABF increased to 139.7% of control value during isoflurane anesthesia, though PVBF and THBF did not change during and after isoflurane anesthesia. Therefore, $\dot{D}hepO_2$ was significantly greater in the isoflurane group compared with the halothane group in the presence of hypoxia. $\dot{V}hepO_2$ was significantly reduced by halothane anesthesia with hypoxia, but was not affected by isoflurane anesthesia. $ChvO_2$ was significantly lower during anesthesia of both groups compared with base line values at control stage, and there was no significant difference between both groups during and after anesthesia. Serum LDH, GOT and GPT were significantly elevated by halothane anesthesia compared with control values, but were not elevated by isoflurane anesthesia four hours after anesthesia.

Discussion. The present study provides that: 1) isoflurane does not decrease hepatic circulation even in the presence of hypoxia, while halothane decreases it seriously at similar decreases of systemic blood pressure; however, 2) there was minimum difference in hepatic oxygen supply-demand relationship between halothane anesthesia and isoflurane anesthesia; and 3) serum hepatic enzyme elevation was seen only in the halothane group. In the present study, hepatic oxygen delivery was maintained better during isoflurane anesthesia than halothane anesthesia, suggesting that there was more oxygen supply to the liver cells during isoflurane anesthesia. This might be the reason why hepatic oxygen consumption was also maintained at a higher level during isoflurane anesthesia compared with halothane anesthesia, since below the critical level of oxygen supply, tissue oxygenation is inadequate, and hepatic oxygen consumption falls proportionally with oxygen supply. Nevertheless, why didn't $\dot{D}hepO_2/\dot{V}hepO_2$ and $ChvO_2$ show any significant difference between both anesthesia groups, while they were a little lower in the halothane group? One possible explanation is that halothane, by reducing oxygen consumption, increases tissue oxygenation, or otherwise, more serious hypoxemia would be necessary for the differentiation of $\dot{D}hepO_2/\dot{V}hepO_2$ of halothane from that of isoflurane anesthesia. Despite of the similar reduction of hepatic oxygen supply-demand ratio, serum hepatic enzymes were elevated only in the halothane group, which indicates that halothane-induced hepatotoxicity may be produced by a different cause from hepatic hypoxia per se. In conclusion, effects of isoflurane on hepatic circulation and hepatic oxygen metabolism were not considered to be worse than that of halothane, probably resulting minimum hepatic damage even in the presence of hypoxia.

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* This research was done following approval of the Animal Investigation Committee.

Title: PROTECTIVE EFFECT OF NIFEDIPINE ON THE LIVER AGAINST HALOTHANE HEPATOTOXICITY IN RATS

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Introduction. The mechanism of halothane-induced hepatotoxicity is not known at the present time. Although many mechanisms have been postulated, including direct hepatotoxicity or toxic intermediate of halothane, free radicals, hepatic hypoxia or immune response, the exact mechanism is obscure. On the other hand, in the process of cell degeneration and necrosis, the acute changes are considered to be compatible with an important role of an increase in cytosolic calcium (Ca++) concentration. In addition, slow Ca++ channel blocker could have a protective effect on the brain and kidney, and maintenance of low intracellular Ca++ concentration is also necessary in the liver for normal hepatic function. Recently, Gelman and Van Dyke pointed out the possibility that both hypoxia and halothane would increase intracellular free Ca++, and this phenomenon could play an important role in the mechanism of halothane-induced hepatotoxicity (1). The present study examined whether oral administration of nifedipine, one of the slow Ca++ channel blockers, could protect the liver against experimental halothane-induced hepatotoxicity in rats.

Methods. Five groups of 76 male Sprague-Dawley rats, weighing 350-450g were studied. All rats were given phenobarbital in their drinking water (0.2%) for four days. Food was removed for the next 24h while the experiment was conducted. Group H+N(20) and group H+N(100) animals received nifedipine 20μg and 100μg/kg/day in their drinking water for 24h prior to the experiment respectively, and then were anesthetized with N_2-O_2-halothane 0.5% under the condition of hypoxia (FiO_2 0.12) in a Plexiglas box for two hours. Rats in group H+P received polyvinyl pyrrolidone which is the solvent of nifedipine, instead of nifedipine solution. Animals in group H were given nothing except clear water 24h prior to the experiment. Animals in group H+P and group H were anesthetized with halothane and hypoxia in the same way as group H+N(20) and group H+N(100). Rats in group C were given only clear water and were exposed to hypoxia alone. All rats were restored to room air and foods were given ad libitum after anesthesia. Twenty-four hours after anesthesia, all rats were sacrified and their liver specimens were fixed and stained with hematoxyline-eosin (H&E) and Oil-Red O for examination by light microscopy. From a single section of liver a progression of up to 10 microscopic fields was scanned. Each field was rated as to the type and degree of morphological change, according to the following scale: 0= normal, 1=mild cellular disruption (some dissociation of centrilobular hepatic cord), 2= moderate cellular disruption (centrilobular degeneration in every microscopic field), 3= extensive centrilobular degeneration, and 4= extensive centrilobular degeneration with centrilobular necrosis. Then, according to the existence of centrilobular cell degeneration, the slides were also graded as being positive or negative. Data were statistically analized with analysis of variance followed by least significant difference test or χ^2-test. $P < 0.05$ was considered statistically significant. This experiment was done following approval of Animal Inv. Committee.

Results. Mean histology score graded from 0 to 4 were 0.2 in group C, 2.05 in group H, and 2.00 in group H+P, while they were 1.09 both in group H+N(20) and group H+N(100). Score in group H+N(20) and group H+N(100) were significantly lower than those of group H and group H+P. Furthermore, positive or negative grading was also significantly lower in group H+N(20) and group H+N(100), compared with group H and group H+P. Eighty-nine percent of the rats in group H and 90 percent in group H+P showed centrilobular degeneration, but administration of nifedipine reduced the incidence to 27 percent in group H+N(20) and 18 percent in group H+N(100), respectively (Fig).

Discussion. This study demonstrates the evidence that oral administration of nifedipine prior to anesthesia could prevent the incidence of halothane-induced hepatotoxicity in enzyme-induced rats, probably through the mechanism of interfering with the influx of Ca^{++} through the ionic channel of the hepatocyte membrane, resulting in prevention of the increase in cytosolic Ca^{++} concentration. However, another theory indicates that Ca^{++} released from intracellular stores plays a more important role in the increase in cytosolic Ca^{++} concentration (2). Halothane could inactivate active Ca^{++} transport by endoplasmic reticulum and could induce rapid glycogenolysis followed by hepatic cellular degeneration in vitro (3). There would be a possibility that nifedipine also affects intracellular Ca^{++} transport inactivated by halothane anesthesia.

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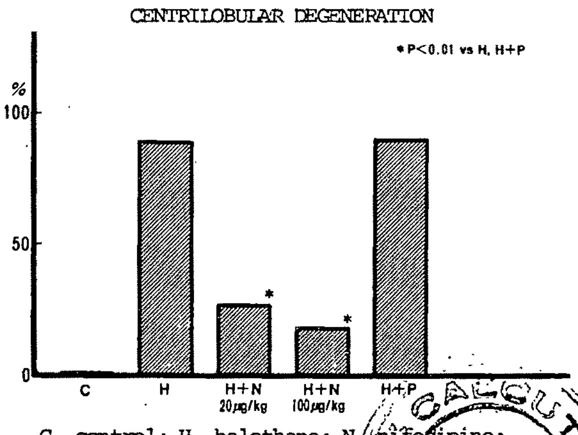

C, control; H, halothane; N, nifedipine;
P, polyvinyl pyrrolidone.

CALCUTTA CENTRAL

Title: EFFECT OF HYPERVENTILATION ON THE PHARMACODYNAMICS OF SUFENTANIL IN MAN

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Introduction. Hyperventilation results in an increased brain concentration of morphine (1) and fentanyl (2) in dogs. This study was undertaken to determine the actions (dynamics) of low-dose sufentanil in both eu- and hyperventilated patients, employing computer analysis of the electroencephalogram (EEG).

Methods. After obtaining institutional approval and informed consent, 22 patients ranging in age from 19 to 62 yr were studied. There were 4 groups: 1) euventilation without narcotic (n=4); 2) hyperventilation without narcotic (n=6); 3) euventilation with sufentanil (n=6); 4) hyperventilation with sufentanil (n=6). All were ASA Class 1 or 2 and had no hepatic or renal disease. None had received narcotics for 1 wk prior to the study. Premedication consisted of glycopyrrolate, 0.2 mg im, 45 to 60 min prior to the induction of anesthesia. EEG leads were placed in the F_3-C_3 and P_3-O_1 positions. The data collection system consisted of a modified power spectral analysis (PSA) device which digitizes the EEG signal, performs a Fast Fourier transformation (FFT) and transfers the FFT data to a Mac Plus computer for storage. Anesthesia was induced with thiopental 4 mg/kg, followed by succinylcholine 1 mg/kg and tracheal intubation. Anesthesia was maintained with nitrous oxide-oxygen (70-30%) and vecuronium. Once a steady-state EEG was observed, reflective of the fast activity typical for 70% N_2O, the study was begun. In all groups when steady-state ventilation was achieved, an arterial blood gas was drawn for $PaCO_2$. Group 1 (euventilation) - The end-tidal CO_2 ($ETCO_2$) was adjusted between 35-38 mmHg and data collected. Group 2 - Euventilation was achieved as in Group 1, and following 5 min of data collection the ventilation was increased to achieve an $ETCO_2$ 20-24 mmHg. The steady-state hyperventilated EEG was compared with the euventilated state to determine the effects of hypocarbia alone on the EEG. Group 3 - Steady-state euventilation was achieved and at this point sufentanil 0.1 ug/kg was given iv, the initial euventilatory state being taken as control. Group 4 - Steady-state hyperventilation was achieved ($ETCO_2$ 20-24 mmHg) and sufentanil was administered as in Group 3, the initial hyperventilated state being taken as control. The stored FFT data was then further processed to derive a total of 25 spectral descriptors of power and frequency.

Descriptors obtained from 15 averaged 2-sec epochs (30-sec time periods) were employed to analyze degree of change in the study groups. These data were then normalized for comparison between patients by taking the control value for each descriptor as 100. A change in any descriptor of at least 10% from control was considered significant. To determine onset time of narcotic action and time to maximum effect, descriptors from 2-sec epochs were examined sequentially. Comparisons between normalized EEG descriptors and between times of onset and maximum effect was made by applying Student's t-test for unpaired data. P 0.05 was considered significant.

Results. The $PaCO_2$ of the euventilated patients (Groups 1, 3) was 40 ± 3 mmHg (mean ± SD) and for the hyperventilated patients (Groups 2, 4) 24 ± 2 mmHg. The euventilated, Group 1, achieved a steady EEG state 15 to 18 min after induction of anesthesia and the EEG descriptors did not vary more than 10% subsequently. The hyperventilated, Group 2, demonstrated increased power in the delta (0.5-3.5 Hz), theta (3.5-7.5 Hz) and alpha (7.5-13 Hz) frequency bands with the greatest increase in the theta band (60%). There was decreased power in the beta band (13 Hz and up). The peak power frequency and the spectral edges from 50 to 97% were all decreased. A derived parameter, delta + theta/alpha + beta, designed to emphasize power shift into the lower frequencies showed the greatest increase (90%). In Groups 3 and 4, the administration of sufentanil caused a greater than 10% change in most of the normalized descriptors, in a direction reflecting a shift of power into the lower frequency range. When the percent change in the various parameters in the eu- and hyperventilated patients (Groups 3 and 4) who received sufentanil were compared at 5, 10 and 15 min, there was no statistically significant difference between these two groups, although the change in the mean values of the normalized descriptors in the hyperventilated group who received sufentanil was always greater than the euventilated group. Mean onset times following the injection of sufentanil ranged between 18 and 51 seconds for the various descriptors with maximum effect achieved between 252 and 332 seconds. There was no significant difference for these times between the eu- and hyperventilated groups.

Discussion. Slow wave activity of the EEG with hyperventilation was first reported by Geddes and Gray in 1959 (3). The fact that most of the EEG descriptors employed in this study changed significantly with hyperventilation to reflect a shift of power into the lower frequency range suggests that descriptors of EEG power and frequency derived from power spectral analysis may provide a sensitive method of quantifying the EEG changes observed with hyperventilation. This same system also proved very responsive to low doses of sufentanil.

This study did not demonstrate any difference in the EEG effect of sufentanil between euventilated and hyperventilated patients. In contrast, animal studies (1, 2) employing morphine and fentanyl have demonstrated that hyperventilation causes an increase in narcotic concentration in the brain when compared with euventilated animals. This suggests that hyperventilation in man may either not cause an increase in brain narcotic concentration or if this effect does occur, it does not appreciably change the patient's EEG response. A third possibility is that sufentanil differs from morphine and fentanyl in its effect on the EEG.

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Title: PHARMACOKINETICS AND PHARMACODYNAMICS OF VECURONIUM IN THE OBESE SURGICAL PATIENT

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Introduction. A recent study has demonstrated that the action of vecuronium is prolonged in obese patients and that this action is closely correlated with increasing obesity (1). In that study, vecuronium concentration was not measured. The authors could only speculate that impaired hepatic clearance and/or an overdose effect with recovery occurring in the redistribution phase were the two most likely causes for the prolonged action of vecuronium. The current investigation of the pharmacokinetics and pharmacodynamics of vecuronium in obese surgical patients was undertaken to clearly define the causes for the prolonged action of vecuronium in the obese.

Methods. Five obese and five control patients of normal weight undergoing a variety of neurosurgical procedures were studied after obtaining informed consent with institutional review board approval. Obese patients were at least 130% of ideal body weight (IBW) based on the formula of the Metropolitan Life Insurance Co. Percent body fat was estimated by the method of Gubner (2). Patients were excluded if they had cardiac, hepatic, renal or neuromuscular disease, or if they were taking medications known to affect neuromuscular transmission. General anesthesia was induced with intravenous thiopental and maintained with nitrous oxide/oxygen and halothane by mask, during which time baseline twitch tension of the thumb was established with a Grass force-displacement transducer (FT-10) by ulnar nerve stimulation of the wrist with surface electrodes using supramaximal stimuli from a Grass stimulator (Model S8) in conjunction with Grass stimulation isolation units. Responses to single stimuli of 0.15 ms duration delivered at a frequency of 0.1 HZ were recorded. After 10 minutes of steady baseline twitch tensions, 0.1 mg/kg of vecuronium was administered intravenously as a bolus and the trachea was intubated. Thereafter mechanical ventilation was maintained with moderate hyperventilation (ET CO_2 26-30 mmHg) employing a mixture of N_2O-O_2 (70-30%) and halothane (0.5-0.6%, end tidal). Core temperature was maintained in all patients between 35.4 and 36.9°C with the aid of warming blankets. Blood samples were obtained from the arterial catheter 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 150, 180, 210 min; and at 4, 5, 6 hr. Additional samples were drawn between the timed kinetic samples if return of twitch warranted obtaining another sample. The plasma was then separated and frozen until analyzed by a spectrofluorometric method.

The times to 5, 25, 50 and 75% recovery of twitch height were recorded. Plasma concentration-time course curves for each patient were fitted to both bi- and triexponential equations, using weighted, nonlinear least squares regression analysis. The best fit for the data was then determined using the F ratio test. Pharmacokinetic parameters were calculated by using standard methods for bolus iv injection of a drug. Clearances and volumes of distribution are presented both in terms of ideal body weight and per kg. These parameters are converted to ideal body weight by multiplying the results per kilogram by total body weight in kg and then dividing by the patient's IBW. Pharmacokinetic parameters, the time to 50% recovery and the recovery indexes (5-25% and 25-75%) were compared between obese and controls by Student's t-test (two-tailed). $P < 0.05$ was considered significant. The linear portions of the log plasma concentration-response curves between 20% and 80% paralysis between the two groups of patients were compared by analysis of covariance.

Results. The control group's age was 44.5 ± 14 yr (mean ± SD), weight 62 ± 9 kg, % IBW 112 ± 9, and % fat 17 ± 4. The obese group's age was 52.4 ± 15 yr, weight 94 ± 15 kg, % IBW 185 ± 30 and % fat 51 ± 12. Plasma decay curves for vecuronium in both groups were best described by biexponential equations. The obese patients demonstrated a significantly longer time to recovery of 50% twitch and a prolonged recovery index (25-75%) (Table 1). Kinetically the obese exhibited a more prolonged elimination half life ($t_{½}$ elim), decreased plasma clearance (Clp) and when calculated in terms of each patient's IBW an increased volume of distribution (Vd_{area}). Comparison of the plasma concentration-response relationship for vecuronium showed no significant difference between obese and control patients.

Discussion. The elimination of vecuronium is highly dependent on hepatic clearance, 40 percent being excreted in the bile in the first 24 hours (3). Thus the observed decreased clearance of vecuronium in the obese is not unexpected since occult abnormal liver histopathology has been documented in the obese despite normal liver function (4). In addition, obese patients may have a decrease in hepatic blood flow (5). The fact that the volume of distribution of vecuronium corrected to IBW is significantly increased in the obese suggests that there is significant distribution of this muscle relaxant into fatty tissue. This study demonstrates that the cause of the prolonged action of vecuronium in the obese is altered pharmacokinetics of the drug in these patients.

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Table 1. Vecuronium Kinetics and Dynamics (Mean ± SD)

	Control, n=5	Obese, n=5	P
$t_{½}$ elim (min)	40.9±6	106.6±50	< .05
Clp (ml·kg^{-1}·min^{-1})	6.8±1	3.1±0.6	< .05
Clp (ml·kg^{-1} IBW·min^{-1})	7.9±1	5.7±1	< .05
V_i (ml·kg^{-1})	96.2±59	78±25	NS
V_i (ml· kg^{-1} IBW)	112±69	140±28	NS
Vd_{area} (ml·kg^{-1})	400±92	384±57	NS
Vd_{area} (ml·kg^{-1} IBW)	465±109	702±101	< .01
T 50% recovery (min)	42.2±9	73.8±1	< .005
T 25-75% recovery (min)	15±5	37.8±13	< .05

Title: THE RELATIONSHIP BETWEEN HEART RATE AND MYOCARDIAL ISCHEMIA IN NONCARDIAC SURGICAL PATIENTS

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Introduction. Myocardial infarction is a major cause of postoperative mortality in noncardiac surgical patients. The cause of postoperative myocardial ischemia and infarction is not known. Recent studies in patients undergoing coronary artery bypass grafting (CABG) suggest that increases in heart rate (HR) are related to myocardial ischemia.[1,2] We therefore examined HR and its relationship to ischemia in the perioperative period in noncardiac surgical patients.

Methods. Twenty-three patients undergoing major noncardiac surgery were prospectively studied with IRB approval and informed consent. HR and ST-segment (real-time analysis) were continuously measured and recorded preoperatively (PREOP), intraoperatively (INTRAOP), and postoperatively (POSTOP) using a portable electrocardiographic monitor (QMED; modified V-5 lead). Medical, surgical, and anesthetic (fentanyl-inhalational general anesthesia) management was not altered by the study. HR was analyzed for the 3 perioperative periods by averaging 15-minute median heart rate samples. High heart rate (HI-HR) was defined when median HR exceeded resting HR by 20% for 15 minutes. Myocardial ischemia was defined by a horizontal or downsloping ST-segment of 0.1 mV (1 mm) or more, 60 msec following the J-point lasting for >1 minute.

Results. Patients were studied for a median period of 15 hrs PREOP, 2 hrs INTRAOP, and 49 hrs POSTOP. Heart rate was maximal POSTOP (87 ± 1 min^{-1}) and minimal INTRAOP (69 ± 1 min^{-1}), Fig 1. Ischemia occurred in 8 patients (27%). A total of 157 ischemic events occurred (total duration 58 hrs, average duration 22 mins). Only 1 ischemic episode was associated with angina. The onset of 135 ischemic events (86% of all ischemic events) was with HI-HR ($p=0.001$ vs onset without HI-HR). There were only four INTRAOP ischemic events (3% of all ischemic events), one of which was related to hypotension (systolic blood pressure < 20% baseline) and bradycardia. A typical case of preoperative ischemia and ischemia subsequent to extubation associated with increases in HR is shown in Fig 2. The relationship of HR to ischemia in individual patients is shown in Table 1. There was a wide range (13-60%) of mean increases in baseline HR to onset of ischemia. The mean minimum increase in HR to ischemia onset was 24% (range: 1-44%).

Discussion. These data show an association between increased HR and myocardial ischemia in noncardiac surgical patients. Hypotension has also been associated with perioperative cardiac events in noncardiac surgical patients.[3] We did not study the effects of blood pressure. The low incidence of INTRAOP ischemia in our study may be related to the low HR and diminished oxygen demand associated with the general anesthesia technique that was used.

HR threshold for angina is known to be variable (83-152 min^{-1}) in patients with ischemic heart disease.[4] Atrial pacing demonstrates a mean HR threshold for angina of approximately 50% above resting HR, similar to our observation in surgical patients with silent (asymptomatic) ischemia. Our finding that HR is well controlled PREOP and INTRAOP, but not in the POSTOP period, is similar to that for patients undergoing CABG.[1] Although tachycardia is the most common hemodynamic abnormality associated with perioperative ischemia in CABG patients, the majority of ischemia in these patients is unrelated to hemodynamic change.[2] Our data suggest that in patients undergoing noncardiac surgery, the majority of ischemia is related to increases in heart rate. Ischemia may also be associated with minimal increases in HR.

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Fig1- PERIOPERATIVE HR (mean ± SEM)

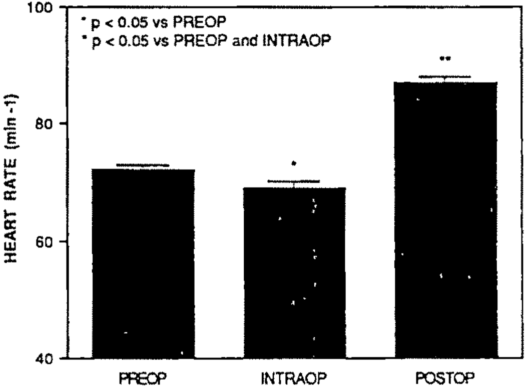

FIG2

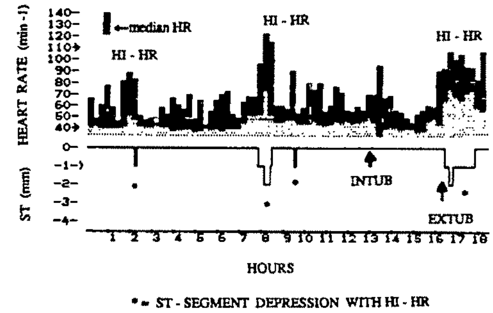

Table 1

PATIENT	BASELINE HR (min^{-1})	HR AT ONSET OF ISCHEMIA (mean ± SD; min^{-1})	% INCREASE IN HR TO ISCHEMIA ONSET (mean ± SD)
1	55	79 ± 12	37 ± 22%
*2	75	82 ± 11	13 ± 13%
3	55	83 ± 9	52 ± 17%
4	75	120 ± 5	60 ± 7%
5	65	100 ± 26	53 ± 39%
6	75	113 ± 3	41 ± 19%
7	70	95	36
*8	65	91 ± 4	43 ± 4%
All Patients:	67 ± 8	96 ± 14	42 ± 14%

HR = heart rate; * on beta-blocker

Title: ACTIONS OF NEOSTIGMINE AT THE MOUSE MOTOR NERVE TERMINAL

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Introduction. Neostigmine, an anticholinesterase, is used to reverse paralysis induced by nondepolarizing blocking drugs. In addition to inhibition of acetylcholinesterase producing postjunctional effects, other mechanisms may be involved in the antagonism of neuromuscular blockade. 1. The increased concentration of acetylcholine at the motor end plate, may produce firing of the motor nerve terminal 2. Anticholinesterase drugs themselves may directly depolarize the motor nerve terminal producing repetitive end plate potentials corresponding to the repetitive firing in the nerve. 3. Anticholinesterase drugs may directly convert a single axonal depolarization into a repetitive response (3). This investigation was carried out to assess the effects of neostigmine on the extracellular action potential (recorded from the) nerve terminal and on the release of acetylcholine.

Methods. Experiments were performed on the left triangularis sterni nerve-muscle preparation isolated from 17-22g male Balb C mice. The preparation was pinned thoracic side downwards to the base of a 2-3 ml tissue bath and perfused at a rate of 5-10 ml/min with the physiological solution described above. For extracellular recording d-tubocurarine (14-37 μM) was added to abolish postsynaptic activity. For intracellular recording the physiological solution contained 0.2mM Ca^{++}. Experiments were performed at 18-23°C. The intercostal nerves were stimulated via a suction electrode every 2 sec with pulses of 50 sec duration and supramaximal voltage. Nerve terminal action potentials were recorded by a glass microelectrode (filled with 2M Nacl, resistance 5-15 megohms) placed inside the perineural sheath (near endplate areas) of one of the branches of an intercostal nerve (5). End plate potentials (E.P.P.s) and miniature end plate potentials (M.E.P.P.s) were recorded by a glass microelectrode (filled with 3M KCl, resistance 10-20 megohms). The potential difference between the silver/silver chloride reference electrode in the bath and the recording electrode was measured by a high impedance unity gain electrometer (W-P Instruments, model M-701), displayed on a dual beam storage oscilloscope and simultaneously stored on FM tape. Usually 20-25 nerve terminal action potentials, 40-50 E.P.P.'s, and 200-300 M.E.P.P.'s were recorded at each time period. Signals were monitored continuously from the same site before and throughout application drugs.

Results.
Extracellular Recording; Neostigmine at 1μM produced a decrease in the second negative component of the waveform, associated with potassium and calcium currents at the nerve terminal, without altering the first negative deflection, which is associated with the neuronal sodium current. Higher concentrations, (up to 400 μM of neostigmine), caused a progressive decrease in the amplitude of the second negative deflection (Fig. 1). This decrease in the second negative component was also present in absence of calcium with neostigmine.

Intracellular Recording; Neostigmine at 0.5μM and 1μM increased the frequency, amplitude, and time to 50% decay of M.E.P.P.s. The amplitude, and time to 50% decay of E.P.P.s were also increased with these concentrations. The quantal content increased by 153% and 373% with 0.5 and 1μM neostigmine respectively. At higher concentrations of neostigmine (10μM) M.E.P.P.s and E.P.P.s were abolished.

Discussion. Recordings of motor nerve terminal action potentials shows that neostigmine reduced the second negative deflection, which represents the local voltage changes generated by inward Ca^{++} and outward K^+ currents at the motor nerve terminals. A reduction in this component of the waveform could indicate increased entry of Ca^{++} into the nerve terminal and/or a reduction in the efflux of K^+ ions. Both of these explanations could account for the increase in quantal content as seen with the intracellular recording. However, the results of the experiments in zero Ca^{++} indicate that the second hypothesis is more likely. It may be concluded that neostigmine (at 0.5-1μM) in addition to its anticholinesterase activity may also antagonize the action of the nondepolarizing neuromuscular blocking drugs by increasing the release of acetylcholine by blocking potassium channels in motor nerve terminals. However, higher concentrations of neostigmine (10μM) results in blockage of acetylcholine receptor as evidenced by the reduction of the amplitude of both E.P.P.'s and M.E.P.P.'s which masks the continuing effect of the potassium channel blockade.

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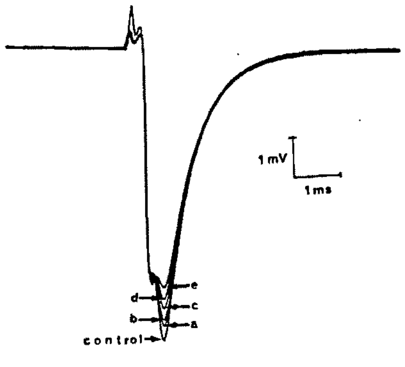
Fig. 1. Effect of neostigmine on extracellularly recorded perineural waveform in 2.5 mM calcium. A,b,c,d and e are waveforms after addition of 1,10,100,200, and 400 μM of neostigmine. Note: reduction in second negative waveform.



Title: DELIBERATE INJECTION OF AIR INTO THE CANINE EPIDURAL SPACE: A RADIOGRAPHIC STUDY

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Introduction. A recent case report has suggested that use of the loss of resistance (LOR) to air technique used to identify the epidural space can lead to epidural air bubbles and therefore contribute to patchy analgesia (1). The mechanism by which this occurs presumably relates to epidural air bubbles large enough and located in close proximity to nerve roots, impeding transfer of local anesthetics across the dura. Because of the almost universal use of LOR to air in epidural anesthesia, and because of the controversy which this case report has generated, (2,3) we designed a study in chronic dogs to determine if and, to what extent, air deliberately introduced into the epidural space forms bubbles, and if so, how long they persist.

Methods. After receiving approval from our Lab Animal Review Board, six female mongrel dogs (20-27 kg) underwent cannulation of the epidural space under a brief thiopental (15 mg/kg) anesthetic. With the dog in the lateral decubitus position, a 17 gauge Tuohy needle was inserted in a sterile fashion via a midline approach in the 6th or 7th lumbar interspace. LOR with 0.9% NaCl (saline) was used to identify the epidural space. Five ml of contrast material (Isovue 300 Squibb) were injected into the epidural space. A-P and lateral radiographs were taken. These films were "no air" controls.

One month later, (Day 1) the same procedure was repeated, except that 3ml of air were injected into the epidural space after LOR to saline, and then followed by 5 ml of contrast. On Days 2,4, and 8 the procedure for the "no air" control experiments was repeated. Radiographs were taken on all days, and were read for the presence or absence, quantity, and location of air bubbles by a neuroradiologist, who used the "no air" films as a reference. He was not aware which of the experimental films were taken following air injections.

Results. Air bubbles were seen in radiographs of all 6 dogs taken on Day 1 and in 3 of 6 dogs taken on Day 2. No air was seen on films taken on subsequent days. Air bubbles seen were relatively few in number and small in size. No predilection for any particular region in the epidural space was noted.

Discussion. The epidural space of dogs of this size (20-27 kg) is relatively small in comparison to that of the adult human, as injection of 10 ml of local anesthetic at L6/7 results in a T_1 level of block (4). Considering this small epidural space, 3 ml of air resulted in few small bubbles, and these bubbles did not seem to localize in any particular region of the epidural space, for example near nerve roots.

Philip recently reported a study in which she deliberately injected 12 ml of air into the epidural space of 63 parturients (5). After subsequent injection of local anesthetic, no cases of patchy analgesia were seen.

Given our results, the results of Philip, and the rare occurrence of patchy analgesia despite the widespread use of LOR to air, it appears unlikely that the use of LOR to air using the usual small volume of air (3-4 ml) results in air bubbles large and numerous enough to cause patchy analgesia. However, it should be noted that air injection does result in some bubble formation, and that these bubbles can persist for as long as 24 hours, which could be of some concern if large volumes of air were injected and if N_2O is used as part of the anesthetic.

This study was supported by USUHS grant R08020.

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Title: ANTAGONISM OF THE RESPIRATORY DEPRESSANT EFFECT OF FENTANYL BY NALMEFENE

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Introduction. Nalmefene is a long acting naloxone derivative with an elimination half-life of about 8 hours (1,2). Nalmefene is excreted in the urine, about 5% unchanged and 60% glucuronide. In the present study the antagonism of fentanyl induced respiratory depression by nalmefene has been investigated.

Methods. Fifty five ASA Clasification I and II female patients signed informed consents to participate in this study, approved by our Institutional Review Board. Patients were premedicated i.m.with 0.1 mg/kg morphine sulfate and 0.2 mg glycopyrolate. Anesthesia was induced with the i.v. injection of 3 to 5 mg/kg thiopental, followed by 3 to 15 μg/kg fentanyl and N_2O-O_2 ($FiO_2 = 30\%$) and maintained with the same N_2O-O_2 mixture and 1 to 2 μg/kg increments of fentanyl and 50 mg increments of thiopental. Vecuronium, 100 μg/kg was used to facilitate intubation and 15 μg/kg increments were injected when surgery required muscular relaxation beyond the clinical duration of the intubating dose. Patients were mechanically ventilated (RR 10/min, RMV 10 ml/kg). At the end of anesthesia, residual neuromuscular block was antagonized by the i.v. injection of a mixture of 30 to 50 μg/kg neostigmine and 0.6 mg glycopyrolate. After satisfactory reversal of the neuromuscular block N_2O was discontinued, the tracheobronchial tree was cleared of secretions and if the respiratory rate (RR) was less than 18/min, 0.5 μg/kg nalmefene was injected i.v. If RR did not increase to 18 min or more in 2 min, a second dose was injected. Patients were extubated 5 min after the injection of nalmefene or when the RR > 18, whichever occured later. RR, heart rate (HR) and systolic (S) and diastolic (D) blood pressure (BP) were recorded at times indicated in the Table. In addition, HR and BP were recorded every 5 min. The means ± SEM of the observations are presented. Data were statistically analyzed with ANOVA followed by Tuckey's test; $p < 0.05$ was considered significant.

Results. The patient's age was 42.4±1.6 (21-72) years and their weight was 65.0±1.5 (45 to 90)kg. The "induction" dose of fentanyl was 6.23±0.35 (3 to 15) μg/kg. The duration of anesthesia was 2.5±0.2 (0.8 to 10.0) hours and the total dose of fentanyl was 5.29±0.27 (2.6 to 10.4) μg/kg/hr. The administration of fentanyl decreased the RR ($p< 0.001$) (see table). HR was lower than control ($p < 0.05$) 5 min after the initial dose of fentanyl and 30 to 60 min after nalmefene and higher than control at 2 and 5 min after nalmefene. S and D BP were also lower at 5 min after administration of fentanyl ($p< 0.05$). At the end of anesthesia, both HR and S and D BP were similar to control. At this time, RR was > 18 in 4 patients, these did not receive nalmefene. The RR was 4.6±0.5 (0-11)/min in the other 51 patients. In 38 of these RR increased to 18.9±0.6 (18 to 28)/min after 0.5 μg/kg i.v. nalmefene. The 13 patients in whom at 2 min RR was < 18 (12 to 16) were given a second 0.5 μg/kg increment. At 5 min the RR was > 18 in all but one patient whose RR was 16 at this time. After the administration of a third dose of nalmefene RR increased to 20 in this patient. Of the 51 patients 2 had severe pain requiring i.m. meperidine between 30 and 60 min after the administration of nalmefene. Of the remaining 49 patients, 27 complained of moderate pain. This could be controlled with one or two 325 mg acetaminophen suppositories. Nausea and or vomiting occured in the recovery room in 8 patients. Two of these required no treatment, 5 were relieved by 10 mg i.m prochlorperazine and in one by 3.75 mg i.v.droperidol.

Discussion. Fentanyl caused profound depression of the respiratory rate in 51 out of 55 patients. This could be promptly and reliably antagonized by one 0.5 μg/kg dose nalmefene in 38, by 2 doses in 12 and by 3 doses in one patient. During the 2 hour observation period in the recovery room, the RR remained satisfactory. Twenty seven (53%) of the 51 patients who received nalmefene had moderate to severe pain. The incidence of pain was 69% in patients who received 2 or 3 doses of nalmefene and 48% in those who received one dose. These differences, however, are not statistically significant. The incidence of nausea and emesis does not seem to be increased by nalmefene. The findings presented indicate that nalmefene is a rapidly acting long lasting antagonist of fentanyl induced respiratory depression.

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The effect of fentanyl followed by nalmefene on respiratory rate, heart rate and blood pressure

Time of Observation	Respiratory Rate	Heart Rate	Blood Pressure Systolic	Blood Pressure Diastolic
Before Induction	17.9[1]	86.9	124.1	75.1
After Fentanyl				
2 min	11.2[2]	88.8	121.0	74.9
5 min	10.2[2]	78.2[2]	107.0[4]	68.0[4]
Before Nalmefene	4.6[2]	87.2	127.2	80.8
After Nalmefene				
2 min	18.9	96.9[3]	137.1	84.8
5 min	20.3	96.9[3]	137.1	84.8
30 min	19.5	76.6[2]	136.6	84.9
60 min	17.7	72.9[2]	131.6	80.5
90 min	18.3	73.4[2]	125.4	75.5
120 min	17.9	75.2[2]	125.4	75.5

[1] Means of 55 observations, before nalmefene, 51 observations at 2,5 and 30 min, and 49 observations from 60 to 120 min after nalmefene. For explanaion see results. SE not given because of lack of space.

[2] Lower than control at the $p< 0.05$ level.

[3] Higher than control at the $p < 0.05$ level.

[4] Systolic and diastolic BP 5 min after fentanyl lower than those at 2 to 30 min after nalmefene.

Title: CEREBRAL EFFECTS OF SUFENTANIL IN DOGS WITH REDUCED INTRACRANIAL COMPLIANCE

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Introduction. It has recently been reported that sufentanil is unique among the narcotics in that the administration of a bolus dose of sufentanil produces a significant increase in cerebral blood flow (CBF) which is accompanied by a significant decrease in cerebrovascular resistance (CVRI) (1). There was no accompanying increase in intracranial pressure (ICP) but none was expected because the dogs had normal intracranial compliance. It was hypothesized that in the presence of decreased intracranial compliance this sudden increase in CBF might be detrimental because it might be accompanied by an acute increase in ICP resulting in cerebral ischemia. The purpose of the present study was to determine the effect of sufentanil on CBF, CVRI, ICP, and cerebral metabolism (CMRO$_2$) in dogs with increased intracranial pressure.

Methods. Following approval by the institutional animal care and use committee, 7 dogs were anesthetized with 0.9% halothane, 70% N$_2$O in O$_2$. Ventilation was controlled to maintain normocarbia. Cannulae were placed in a femoral artery for blood sampling and pressure measurement and into the posterior sagittal sinus for continuous measurement of CBF and calculation of CMRO$_2$. An 8 French Fogarty® venous thrombectomy catheter with a balloon capacity of 4.0 ml was inserted into the left parietal epidural space while a fiberoptic device was inserted into the right parietal epidural space for measurement of ICP. Mean arterial pressure (MAP), CBF, ICP, temperature, electrocardiogram, and 4 lead electroencephalogram (EEG) were monitored continuously. Arterial blood gases, hemoglobin, glucose, lactate, and catecholamine levels were measured periodically. All skin and muscle edges of incisions were infiltrated with 0.25% bupivicaine. Following discontinuation of halothane and N$_2$O, steady state control measurements were obtained during N$_2$/O$_2$ ventilation. The ICP was then raised to 25-30 mmHg by instilling saline into the Fogarty® catheter balloon. When the increased ICP remained constant for 15 min, control measurements were repeated. Each dog then received an i.v. bolus of 200 µg/kg sufentanil and all measurements were continued for 1 h. At the end of the study cerebral biopsies were taken for determination of the cerebral energy state by measuring levels of ATP, phosphocreatine, glucose, lactate, and by calculating the energy charge.

Results. Sufentanil produced a significant increase in CBF which peaked at 2 min (116% increase) then gradually decreased but remained above the control CBF throughout the study (Fig. 1). This was accompanied by a significant decrease in CVRI. ICP significantly increased above the increased ICP control value (29 ± 1 mmHg) to a peak increase of 52% at 2 min (44 ± 4 mmHg) and remained significantly increased throughout the study (Fig. 2). Sufentanil produced deep anesthesia on the EEG and a small but significant decrease in CMRO$_2$ (Fig. 3). The cerebral metabolites were normal except in the area of the balloon where the ATP and phosphocreatine were significantly decreased and the lactate was significantly increased indicative of ischemia.

Discussion. This study demonstrates that, in the presence of decreased intracranial compliance, the increase in CBF produced by sufentanil is accompanied by a prolonged increase in ICP which can result in ischemia. Therapy designed to increase intracranial compliance may modify this cerebral response to sufentanil. Until this has been demonstrated, it is recommended that the use of sufentanil-O$_2$ anesthesia be avoided in patients with decreased intracranial compliance.

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Figure 1

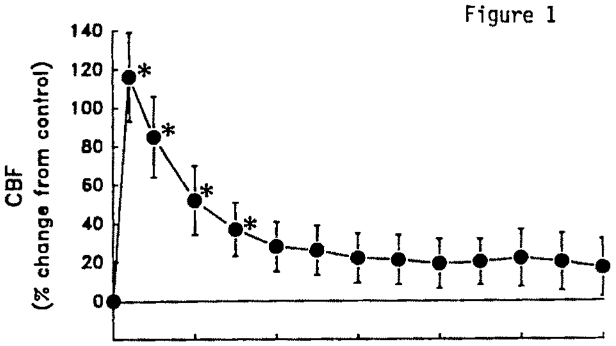


Figure 2

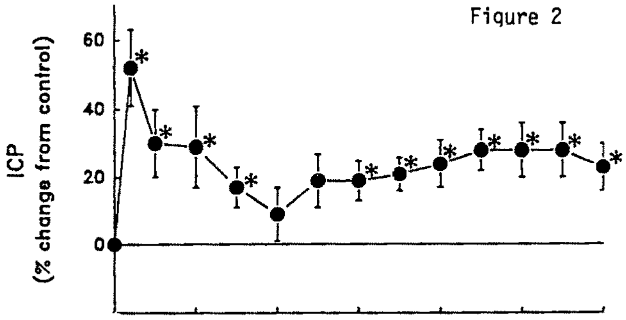
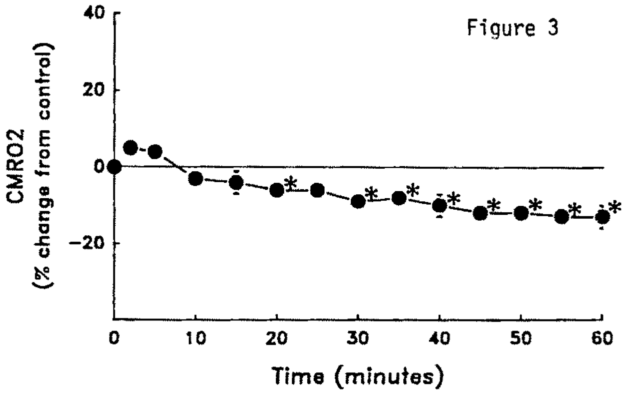


Figure 3



Title: PROPOFOL INFUSION FOR MAINTENANCE OF ANESTHESIA FOR VITREOUS SURGERY: COMPARISON WITH ISOFLURANE

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Introduction The use of propofol, a new non-barbiturate intravenous anesthetic agent is associated with rapid and smooth induction of anesthesia and a rapid and smooth recovery with few side effects and in particular a low incidence of nausea and/or vomiting (1,2). A quick recovery and absence of postoperative nausea and vomiting along with avoidance of nitrous oxide are essential requisites of anesthesia for vitreous surgery with fluid-gas exchange. An alternative to the use of inhalation anesthesia for this type of surgery is the use of intravenous anesthesia by continuous infusion. Propofol (P) has been shown to be a suitable agent for use as a continuous infusion (3,4) and its use has been assessed in the present study for maintenance of anesthesia in patients undergoing vitreous surgery. A control group was anesthetized with isoflurane (I).

Methods Forty adult, ASA I or II patients 20-70 yr were included in the study with their informed consent and approval from the Hospital Ethical Committee. All were to undergo vitreous surgery with fluid-gas exchange. Following premedication with oral diazepam anesthesia was induced with a sleep dose of propofol (usually 1.5 - 2.0 mg/kg) preceded by fentanyl 3 μg/kg. Vecuronium in an initial dose of 0.1 mg/kg followed by further increments was used for muscle relaxation. Oxygen-enriched air was used for ventilation. Twenty patients each were randomly allocated to maintenance of anesthesia by either a continuous infusion of propofol or inhalation of isoflurane. Patients in the infusion group received P at an initial rate of 10 mg/kg/h. The infusion rate was reduced to 8, 6 and 5 mg/kg/h at 30 min intervals unless the depth of anesthesia was considered inadequate. Those in the inhalation group received isoflurane in a concentration necessary for maintaining adequate anesthesia. Neuromuscular block was antagonised at the end of surgery prior to discontinuation of propofol or isoflurane.

Heart rate, arterial pressure, neuromuscular block, end-tidal CO_2 concentration and oxygen saturation were monitored throughout. Stability of heart rate, arterial pressure, absence of any sweating and muscle movements were used to gauge the adequacy of anesthesia.

The times taken to opening of the unoperated eye and for giving the correct date of birth after cessation of propofol or isoflurane were recorded to assess immediate recovery. Side effects such as nausea, vomiting, restlessness, confusion were recorded for 24 h. Patients were visited in the evening of the operation and the next day. Evidence of any awareness under anesthesia was particularly sought at each time.

Results The two groups were comparable in age, weight and the duration of surgery (Table 1). Control of the depth of anesthesia was considered good in 16 patients receiving propofol and in 9 patients receiving isoflurane. The quality of recovery was considered good in 15 patients given propofol and in 10 patients given isoflurane.

Table 1 also shows the times to opening of eye and giving the correct date of birth after stopping anesthesia. Both were significantly shorter in the propofol group. Of greater importance, however, was the quality of recovery and patient co-operation in the immediate postoperative period. Patients in the propofol group were more clear-headed as well as more co-operative in maintaining prone or lateral postures for correct positioning of the gas bubble in the eye. Five patients in the propofol group had nausea in the immediate postoperative period. Nine patients had nausea or vomiting in the isoflurane group. No patient from either group had any recollection whatsoever of any events of the perioperative period. The average dose of propofol used in the infusion group was 0.11 mg/kg/min excluding the induction dose.

Discussion It is considered essential to exclude nitrous oxide from anesthetic gases in patients undergoing vitrectomy and fluid-gas exchange. The patient co-operation in the postoperative period after this type of surgery is important for the success of surgery. The present study showed that these objectives could be met by using continuous intravenous anesthesia with an infusion of propofol in conjunction with a moderate dose of fentanyl, muscle relaxation and controlled ventilation.

The quicker recovery with propofol as shown by opening of eye and giving the date of birth was confirmed in the present study. In addition the quality of recovery in terms of clarity of thought and patient co-operation were also evident. An added advantage of the technique is avoiding theatre pollution.

Table 1. Age, weight and recovery characteristics

	Propofol Infusion	Isoflurane
Age (yr)	45 ± 18.9	45 ± 16.9
Weight (kg)	72 ± 11.9	74 ± 13.9
Duration of surgery(min)	144 ± 27.5	150 ± 35.0
Time (min) to:		
Opening eyes*	9.4 ± 5.3	15.6 ± 12.0
Date of Birth*	11.1 ± 5.2	17.6 ± 12.0

* $p < 0.05$ between groups Values are mean ± SD

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Title: EFFECT OF CHRONIC ANTICONVULSANT THERAPY ON RECOVERY FROM ATRACURIUM

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Introduction: Chronic anticonvulsant therapy has been alleged to accelerate recovery from the neuromuscular blocking effects of both long-acting muscle relaxants and vecuronium. This has been reported in patients receiving either chronic phenytoin (DPH) (1) or carbamazepine (CBZ) (2) alone. However, neither of these reports were able to demonstrate similar findings for atracurium. This study was designed to determine if patients on long-term (years) multiple anticonvulsant therapy will demonstrate resistance to the neuromuscular effects of atracurium.

Methods: Thirty-five consenting patients were studied according to a protocol approved by our institution's Human Studies Committee. Patients with renal, hepatic, cardiopulmonary, or neuromuscular disease were excluded from the study.

Anesthesia was induced with thiopental 4 mg/kg i.v. and fentanyl 3-10 ug/kg i.v. Maintenance of anesthesia consisted of nitrous oxide 70% in oxygen, 0.2-0.3% end-tidal (ET) isoflurane, and fentanyl infusion (2-7 ug/kg/hr). Esophageal temperature was maintained above 35°C and ventilation was controlled to an ET-CO_2 between 20-30 mmHg. The ulnar nerve was stimulated indirectly with a Puritan-Bennett/Datex Neuromuscular Transmission Monitor (NMT 221®) via surface electrodes. The NMT 221® delivers a train of four square-wave (100 microsecond width) supramaximal impulses at 2 Hz. The resulting evoked compound electromyogram (EMG) of the adductor pollicis is then recorded. Immediately after induction of anesthesia, the baseline EMG was recorded. Following facilitation of tracheal intubation with atracurium 0.5 mg/kg i.v., the train of four was repeated every 20 seconds and the NMT 221® measured the T-1 and TR values where: T-1%=(first EMG response/baseline EMG) X 100 and TR%=(fourth EMG response/first EMG response) X 100. The times (min) for recovery of T-1 to 25, 50, 75, and 90% were recorded, as were the times for recovery of TR to 25, 50, 75, and 95%.

The patients were retrospectively divided into three groups based on their anticonvulsant medication history: MED=0--12 control patients undergoing various neurosurgical procedures who were not on any anticonvulsants. MED=1--11 patients undergoing craniotomy for seizure focus excision who were on chronic CBZ for years. MED=2--12 patients also for seizure focus excision who were on chronic CBZ plus either chronic DPH or valproic acid therapy for years. All serum anticonvulsant levels were in the therapeutic range prior to surgery. The EMG findings in the three medication groups were compared using analysis of variance and a p<0.05 was considered statistically significant.

Results: The three study groups were comparable with respect to age, weight, sex, and premedication. At each T-1% (Table 1) and TR% (Table 2) level, the time (mean values ± SD) required for the patients on long-term anticonvulsant therapy (MED=1 and MED=2) to recover from atracurium induced neuromuscular blockade was significantly shorter compared to the non-treated control group (MED=0). A highly significant difference (p<0.01) in recovery time was demonstrated at each TR% level. This was not found at any T-1% level.

Discussion: Our results do not agree with the findings of earlier studies. This could be due to differences in both the amount and duration of anticonvulsant therapy. In the previous investigations, the study populations were receiving single anticonvulsant regimens for one month or less (1, 2, 3), whereas our epileptic patients were on one or more of these drugs for years. The data in Tables 1 and 2 indicate that there is a dose-effect relationship between the number of long-term anticonvulsants received and the rate of TR and T-1 recovery. Both CBZ and DPH have been shown to decrease prejunctional release of acetylcholine (4, 5). A similar presynaptic effect has been described for atracurium (6). Continual presynaptic inhibition of acetylcholine release by long-term administration of anticonvulsants could result in a state of receptor hypersensitivity such that the effect following subsequent exposure to atracurium is diminished. Our results demonstrate a highly significant difference in recovery at all TR% levels. This was not shown for T-1 and could be consistent with a more pronounced prejunctional drug interaction. Further investigation of the atracurium anticonvulsant drug interaction is warranted.

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TABLE 1: TIME TO RECOVERY OF T-1 IN MIN (MEAN ± SD)

	MEDICATION GROUP			
	Zero(N=12)	One(N=11)	Two(N=12)	p
25%	44±9	42±7	36±5	<0.05*
50%	52±9	48±8	41±5	<0.05*
75%	61±10	54±10	46±7	<0.05*
90%	68±12	60±11	52±9	<0.05*

TABLE 2: TIME TO RECOVERY OF TR IN MIN (MEAN ± SD)

	MEDICATION GROUP			
	Zero(N=12)	One(N=11)	Two(N=12)	p
25%	55±8	48±6	42±6	<0.01**
50%	64±8	55±8	48±6	<0.01**
75%	71±9	61±8	53±6	<0.01**
95%	79±10	67±8	60±7	<0.01**

*p<0.05

**p<0.01

THE EFFECT OF AGE ON POSTOPERATIVE PAIN RELIEF AFTER STANDARDIZED DOSES OF EPIDURAL MORPHINE

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Introduction. It is our clinical experience that elderly patients obtain more effective relief of postoperative pain than do young patients with currently acceptable doses of epidurally administered morphine. The purpose of this study is: 1) to ascertain any differences in pain relief following a single standardized dose based on weight of epidurally administered morphine between young versus elderly patients. 2) to define the pharmacokinetics of absorption of morphine from the epidural space in young versus elderly patients.

Methods. Approval for the study was obtained from our institution's Ethics and Research Committee and informed consent was obtained from each patient. Two groups of patients were studied, Group I, eleven (11) patients aged 65 years or older, and Group II, nine (9) patients aged 50 years or younger. All patients were scheduled for elective abdominal surgery. Patients with significant cardiac, renal or hepatic disease were excluded from the study.

A lumbar epidural catheter was placed prior to the induction of general anaesthesia. The induction and maintenance of anaesthesia were performed without the use of narcotics. Patients received d-tubocurare 3 mg, pentothal 3-5 mg/kg until loss of lash reflex and succinylcholine 1.5 mg/kg for intubation. Anaesthesia was maintained with nitrous oxide in oxygen with the addition of enflurane or isoflurane as needed. The choice of neuromuscular blockers was left to the discretion of the attending anaesthetist. A single dose of preservative-free morphine (0.5mg/ml or 1.0 mg/ml) was given based on a dose of 0.07 mg/kg. The volume of solution injected was made up to a total of 10 mls with preservative-free normal saline, and was administered by the attending anaesthetist shortly after induction of anaesthesia. The first eight patients in each group were selected for the morphine pharmacokinetic profiles. Serial blood samples were drawn from an indwelling arterial canula; the first at zero time, just prior to the morphine administration, and then at 2,5,10,15,30,60,90 and 120 minutes respectively. Serum morphine levels were determined by high performance liquid chromatography.(1) Postoperative pain relief was judged as effective if the patient did not require analgesic supplementation within the first 12 hours after administration of epidural morphine or ineffective if the patient did require supplementation. Differences in systemic absorption of epidural morphine between groups were assessed by two-way analysis of variance for repeated measurements. Dunnet's test was used to determine whether there were significant differences in morphine levels within each group from control (zero time). Fisher's exact test was used to test for significant differences in the effectiveness of analgesia between groups. A p value of < 0.05 was considered significant.

Results. A peak plasma morphine level, 51.1±5.8 ng/ml occurred at approximately 5 minutes in Group I, while in Group II, peaked at 46.3±4.2 ng/ml by 10 minutes.

Plasma Morphine Levels (ng/ml) after Epidural Administration of Morphine

	I 65 yrs	II 50 yrs
0	0	0
2 min	*33.4±5.2	*36.3±9.1
5 min	*51.1±5.8	*43.4±5.8
10 min	*42.3±4.3	*46.3±4.2
15 min	*37.4±4.4	*43.6±5.0
30 min	*25.4±3.0	*28.8±2.2
60 min	*14.6±1.2	*16.6±1.7
90 min	10.9±1.3	12.5±1.6
120 min	8.3±1.3	9.4±1.6

All values reported as mean ± standard error.

Two-way analysis of variance, $p > 0.05$ ($p=0.43$ and 0.87 respectively) shows plasma morphine levels did not differ significantly between groups.

*Dunnet's test within each group $p < 0.05$ for plasma morphine levels of 2 minutes to 60 minutes respectively. Morphine levels at 90 and 120 minutes did not significantly differ from control (zero time) for the sample size.

Pain Relief.

Group (No. Patients)	Effective	Ineffective
I 65 yrs (11)	8	3
II 50 yrs (9)	1	8

$p < 0.05$ Fisher Exact Test (two-tailed)

Significant differences in the effectiveness of pain relief was demonstrated between groups following epidural morphine 0.07 mg/kg.

Discussion. Aging is associated with a steady decline in neural population within the spinal cord. (2) Could the superior pain relief obtained by the elderly group be a reflection of a decreasing population of opiate receptors within the spinal cord? This might result in a higher relative concentration of morphine at the spinal receptor sites and consequently more effective analgesia in the elderly. The minimum effective plasma concentration of morphine for postoperative pain relief is approximately 20 ng/ml. Plasma morphine levels were well below 20 ng/ml after 60 minutes except in two patients. These exceptions were both young patients with ineffective analgesia. The effective prolonged analgesia is due to morphine acting on receptors in the spinal cord.

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TITLE. MORPHINE DISRUPTS NOCTURNAL SLEEP IN A DOSE-DEPENDENT FASHION

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A previous study showed that the first week after abdominal surgery is associated with profound disturbances in nocturnal sleep (1). Among the many factors which alter sleep in this setting, narcotics may play an important role. Morphine given to pain-free volunteers severely disrupts nocturnal sleep, producing changes similar to those observed in the patients studied after surgery (2). The purposes of the present study were to further examine this disturbance of sleep due to narcotic and to assess its relation to narcotic dose.

Methods

The protocol was approved by the Institutional Ethics Review Board and informed written consent was obtained. The subjects were 6 healthy volunteers, 4 males and 3 females, age 22±1 yrs, wgt 71±9 kg and hgt 172±6 cm (means ± S.D.). In every subject, we examined the effects of two doses of morphine, 0.1 and 0.2 mg·kg^{-1}. The studies of each dose were separated by a minimum period of one month.

Both doses were studied in a standardized three night protocol. On the first night, the subject adapted to the sleep laboratory environment. On the second night, the subject received a placebo of normal saline I.M. and on the third night, morphine I.M. To simulate the typical postoperative narcotic routine, the injections were given at 2200 hrs and again at 0200 hrs.

On each night of study, continuous polysomnographic recordings (i.e. EEG, EOG, and EMG) were made from 2300 to 0700 hrs. Sleep was then staged according to standard criteria. We calculated sleep time, awake time (after the initial onset of sleep), the number of awakenings and sleep stages as percent of sleep time. Data for the two placebo nights of each subject were averaged. The statistical assessment was by analysis of variance and the least significant difference test, considering a p value of 0.05 as significant.

Results

The larger dose of morphine, 0.2 mg·kg^{-1}, severely disrupted nocturnal sleep, increasing both the number of spontaneous awakenings and the time spent awake, as well interrupting the normal cycles of sleep (Table). Accompanying these effects were a moderate reduction in slow wave sleep and a severe depression of REM sleep. Indeed, in two subjects, REM sleep was completely eliminated. Amongst individual subjects exposed to morphine, there was a strong correlation between the increased number of awakening and the reduction of REM sleep ($r=0.73$).

The small dose of morphine 0.1 mg·kg^{-1}, produced a similar reduction of slow wave sleep, but no detectable change in the other sleep indices.

Discussion

At a typical analgesic dose of 0.2 mg·kg^{-1}, morphine is a powerful disrupter of sleep, interfering with the continuity of sleep and markedly suppressing both slow wave sleep and REM sleep. The result is superficial and highly fragmented sleep - i.e. insomnia. If given to pain-free patients, morphine at this dose, cannot be considered a hypnotic!

At a smaller dose, 0.1 mg·kg^{-1}, morphine produces relatively little disturbance in nocturnal sleep. The only detectable effect was a modest impairment of slow wave sleep. Thus the principle effects of morphine on sleep appear highly dose-dependent, becoming evident only at doses greater than 0.1 mg·kg^{-1}.

The changes in sleep observed in our pain-free volunteers given morphine 0.2 mg·kg^{-1} are nearly identical to those seen previously in patients during the first nights after abdominal surgery (1). Their apparent dependence on doses greater than 0.1 mg·kg^{-1} suggests that techniques of postoperative pain control which avoid higher blood and brain levels of narcotic (such as patient controlled analgesia or epidural analgesia) merit study.

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Table:

	Placebo	Morphine	
		0.1 mg·kg^{-1}	0.2 mg·kg^{-1}
Sleep time (min)	386±27	418±44	312±91+
Awake time (min)	26±10	37±34	104±64*+
Awakenings (number)	7±3	12±8	30±14*+
Sleep stages (%)			
Stage 1	9±3	12±4	23±3*+
Stage 2	52±6	58±9	58±12
Slow wave	16±5	10±6*	9±7*
REM	22±4	19±4	5±4*+

n = 6, means ± S.D.
* different from placebo ($p < 0.05$)
+ different from 0.1 mg·kg^{-1} ($p < 0.05$)

TITLE. **MORPHINE PRODUCES A DOSE-DEPENDENT RESPIRATORY DEPRESSION WHICH IS POTENTIATED BY NON-REM SLEEP**

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Clincally important respiratory depression due to narcotic seems almost invariably associated with loss of consciousness or sleep. A previous study showed that natural sleep enhances the depressant effect of morphine on the ventilatory response to CO_2 (1). How sleep plus narcotic affects resting breathing has apparently not been investigated. Natural sleep is not a homogeneous state with respect to mechanisms of ventilatory control since breathing in the non-REM stages of sleep is completely dependent upon chemical reflexes whereas in REM sleep it is only partially so. Thus, it is conceivable that narcotics affect resting breathing differently in non-REM and REM sleep states.

The purpose of this study was to define the effects of morphine on resting breathing in both non-REM and REM phases of natural sleep.

Methods

The investigation was approved by the institutional committee and informed written consent was obtained. Six young healthy volunteers were studied while exposed to two doses of morphine, 0.1 and 0.2 mg·kg^{-1}. Exposures to each dose were separated by at least a month.

Each study was conducted over three consecutive nights while the subject slept in a laboratory. On the first night, the subject adapted to the laboratory environment. On the second night, he or she received normal saline I.M. and, on the third night, morphine 0.1 or 0.2 mg·kg^{-1} I.M. Each injection was given at 2200 hrs and repeated at 0200 hrs. At 2300 hrs, the subject retired to bed for the night and from that time until 0700 hrs, the transcutaneous PCO_2 (Radiometer TCM20), respiratory rate (RR, Respitrace) and SaO_2 (Biox II oximeter) were monitored continuously. At 2245 hrs, arterial blood was drawn and the trancutaneous PCO_2 – arterial PCO_2 difference determined in order to convert transcutaneous values observed in sleep to their $PaCO_2$ equivalents. (The measured $PtcCO_2$ – $PaCO_2$ difference was 4±2 mmHg). Sleep was staged according to standard bioelectric criteria (EEG, EOG and EMG). The mean $PaCO_2$ or $PaCO_2$ equivalent, respiratory rate and SaO_2 of each state were then calculated. To allow for the response time of the transcutaneous CO_2 to sleep related changes in $PaCO_2$, the data of the first three minutes after each state change were eliminated from the analysis. The results of the two placebo nights of each subject were averaged. Statistical assessment was by an analysis of variance and the least significant difference test. A p value of 0.05 was considered significant.

Because morphine 0.2 mg·kg^{-1} abolished REM sleep in two subjects, the assessment of this state was made in the remaining group of four.

Results

Morphine produced a dose-dependent increase of $PaCO_2$ during the state of wakefulness, REM sleep, and non-REM sleep. (Table) The increments in awake and REM sleep states were similar, but the increase in non-REM sleep at the 0.2 mg·kg^{-1} dose was consistently greater. Indeed, the effect of morphine 0.2 mg·kg^{-1} together with non-REM sleep on $PaCO_2$ was significantly greater than the sum of the individual effects of morphine alone (i.e. during wakefulness) and non-REM sleep alone (i.e. with placebo), suggesting potentiation.

Morphine reduced respiratory rate during wakefulness, REM sleep and non-REM sleep, but did not induce sleep apneas. Morphine also decreased SaO_2 modestly in all three states.

Discussion

We conclude that morphine is most depressant to breathing in non-REM sleep. This state of sleep appears to potentiate the ventilatory depressant actions of these agents, unlike REM sleep in which the magnitude of effect is similar to that seen in the awake state.

Although the combination of morphine and non-REM sleep did not seriously impair respiration in any of our young healthy volunteers, caution must be exercised in extrapolating these data to other circumstances. In the presence of larger doses of narcotic or when narcotic is given patients who are particularly sensitive, non-REM sleep may act to precipitate severe depression.

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Table:

		Placebo	Morphine	
			0.1 mg·kg^{-1}	0.2 mg·kg^{-1}
$PaCO_2$	Awake	40±3	42±3+	43±3+
	REM	44±3x	46±4x	48±3x
	NREM	44±3x	47±3+x	51±3+*xo
RR	Awake	16±3	13±2+	13±2+
	REM	15±2	13±2+	12±3+
	NREM	14±2x	12±2+x	11±1+*x
SaO_2	Awake	96±1	95±1+	94±2+*
	REM	96±1	95±2	94±2
	NREM	96±1	94±1+x	94±2+

means ± SD
+ different from placebo, same state ($p<0.05$)
* different from 0.1 mg·kg^{-1}, same state ($p<0.05$)
x different from awake, same night ($p<0.05$)
o different from REM, same night ($p<0.05$)

TITLE: CARDIAC ANESTHESIA TECHNIQUES: FENTANYL ALONE OR IN COMBINATION WITH ENFLURANE OR PROPOFOL

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Introduction. The optimal anesthetic technique employed for cardiac surgery should afford easily attainable hemodynamic stability, preserve myocardial oxygen supply-demand ratio and permit a rapid recovery. Early extubation following cardiac surgery enhances initial myocardial performance.[1] High-dose fentanyl anesthesia provides intraoperative hemodynamic stability and does not adversely affect coronary artery blood flow, but the large doses required to blunt the autonomic response to surgery may result in a prolonged recovery and delayed extubation. The more rapidly eliminated anesthetics enflurane and propofol (a new short-acting, intravenous, sedative-hypnotic) may be used as adjuvants to fentanyl anesthesia.[2] The purpose of this study was to compare the intraoperative hemodynamic control and the postoperative recovery following fentanyl alone or in combination with enflurane or propofol.

Methods. Thirty-three consenting adults scheduled for aorto-coronary bypass surgery were studied after obtaining Institutional Review Board approval. All patients were premedicated with morphine sulfate, 7.5-15 mg, IM, scopolamine, 0.2-0.4 mg, IM, and diazepam, 5-15 mg, po, one hour before surgery. Perioperative monitors included ECG, arterial and thermodilution pulmonary artery catheters, and esophageal and rectal temperature probes. Nitroglycerin, 50 µg/min, IV, was administered prior to the induction of anesthesia and throughout the perioperative period. Hemodynamic measurements (heart rate, mean arterial pressure [MAP], cardiac index [CI], systemic vascular resistance index [SVRI] and pulmonary artery occlusion pressure [PAOP]) were recorded prior to and after induction of anesthesia and during anesthetic maintenance. Anesthesia and muscle relaxation were induced with fentanyl, 25 µg/kg, IV and metocurine and pancuronium, 0.08 mg/kg, IV. When the MAP exceeded the post-induction (baseline [BL]) value by more than 15%, patients were randomly assigned to receive one of three treatments for maintenance of anesthesia: fentanyl (F), 0.15-0.45 µg/kg/min (to 150 µg/kg); enflurane (E), 0.25-2.0 percent or propofol (P), 0.05-0.5 mg/kg/min. These drugs were administered to maintain the MAP within 15% of the BL before and after cardiopulmonary bypass (CPB) and within 40-80 torr during hypothermic CPB at a constant flow of 2.1-2.3 L/Min/M^2. Inotropic support was administered on discontinuation of CPB as required to maintain MAP greater than 70 torr. All patients received fentanyl, 10 µg/kg, IV, after weaning from CPB. On the first postoperative day, patients were questioned about intraoperative recall. Data were analyzed using ANOVA and Kruskal-Wallis with p-values <0.05 considered statistically significant. Data are presented as mean ± SD.

Results. There were no significant differences in age, ASA physical status, ejection fraction (EF), aortic cross (X) clamp or total CPB time among the treatment groups (table 1). However, patients in Group F weighed significantly less than patients in Group E or P. Group F patients received fentanyl, 8812 ± 2079 µg (122 µg/kg) and Group P patients received propofol, 789 ± 512 mg (9.4 mg/kg). All treatments were equally effective in achieving and maintaining blood pressure control (figure 1). All group treatments resulted in similar decreases in MAP and CI (table 2). PAOP and SVRI did not change significantly in any group following drug treatments. Patients in all groups had similar inotrope requirements necessary for CPB weaning or long term support. Patients treated with P and E awakened sooner than patients in Group F. Patients in Group F were intubated significantly longer than patients in Groups E or P (figure 2). Intraoperative awareness occurred in only one patient (Group F).

Discussion. In this study, patients anesthetized with enflurane or propofol had a more rapid emergence and were extubated earlier than patients anesthetized with fentanyl alone. Previous studies with propofol and enflurane have demonstrated significant cardiovascular depression, while fentanyl produces minimal myocardial depression.[3] However, in this study, all therapies resulted in comparable decreases in cardiac performance and similar requirements for inotropic support after CPB. Additionally, intraoperative hemodynamic control was comparable in all groups. In conclusion, the shorter acting drugs enflurane or propofol may be preferable in patients suitable for early extubation following cardiac surgery.

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Table 1. Patient characteristics.

	N	Age (yrs)	Weight (kg)	EF (%)	X-Clamp (min)	CPB (min)
F	12	67±5	72±13*	53±10	48±12	92±30
E	10	64±9	83±11	51±12	39±18	72±24
P	11	60±9	84±11	52±11	55±17	82±20

p=0.006 Group F vs Groups E and P

Table 2. Hemodynamic effects of drug treatments (Rx).

	F	E	P
Pre Rx Map (torr)	95±18	91±11	85±11
Post Rx MAP (torr)	83±13	72±8	75±13
Pre Rx CI (torr)	2.7±0.5	2.7±1.0	2.7±0.8
Post Rx CI (torr)	2.3±0.6	1.9±1.6	2.4±0.8

FIG 1. DIFFERENCES IN BP CONTROL

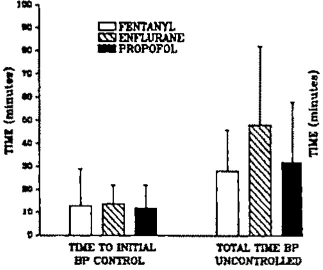
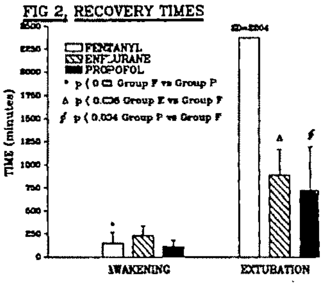


FIG 2. RECOVERY TIMES



Title: PROPHYLACTIC NALBUPHINE IN CAESARIAN SECTION PATIENTS TREATED WITH EPIDURAL MORPHINE

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Introduction. Epidural morphine has been demonstrated to provide effective post-caesarian section analgesia (1-3). The elimination of the risk of delayed respiratory depression would lead to a safer analgesic technique. Nalbuphine effectively reverses narcotic induced respiratory depression without affecting cardiovascular stability or analgesia (4,5). Pruritus, another common side effect of epidural morphine, has been shown to be reversible by naloxone. Nalbuphine, due to its narcotic antagonist properties may well decrease this side effect. Our experience with prophylactic intravenous nalbuphine and its effect on respiratory depression and pruritus after epidural morphine is reported here.

Methods. Following approval by the University of Toronto, Human Subjects Review Committee, patients who were to undergo elective caesarian section were asked to participate in our study if free of cardio-vascular, respiratory, renal or hepatic disease and had no contraindication to epidural anesthesia. Following a preload of 1000-1500 cc of balanced salt solution, epidural anesthesia was instituted with carbonated lidocaine with 1:200,000 epinephrine. After delivery of the baby, 5 mg of epidural morphine in 10 ml was given. At skin closure, 20 mg of nalbuphine or saline was given intravenously followed by 2 doses of 10 mg or saline at six-hourly intervals post-operatively. This was done in a double-blind randomized fashion. Hourly assessment of the patient's vital signs, including respiratory rate, oxygen saturation as measured by pulse oximetry, sedation, pruritus and pain relief by a visual analogue scale were made for 18 hours after epidural morphine administration. Comparison of the data was done using the Student's T and Mann Whitney Tests with $p < 0.01$ being considered significant.

Results. All patients had adequate surgical anesthesia. Both groups were comparable with regards to age and parity. There were no fetal or maternal complications. There were five patients who had evidence of respiratory depression as defined by a respiratory rate less than ten or an oxygen saturation less than 90%. Two of the patients received saline and three received nalbuphine. Comparison of oxygen saturations, respiratory rate, pain, sedation and pruritus showed no statistically significant difference between the saline and nalbuphine groups. Both groups reported good to superior pain relief.

Discussion. 1) Epidural morphine provides effective post-caesarian section analgesia which was unaffected by intravenous nalbuphine.
2) Respiratory depression occurred in 5 patients with no difference between the nalbuphine and saline groups. This depression appeared to have no relationship to the time after epidural morphine injection. 3) Nalbuphine neither reverses pruritus nor does it improve respiratory rate or oxygen saturation following epidural morphine. 4) This data indicates that nalbuphine has no effect on post-operative respiratory depression after caesarian section. It would therefore be unlikely to provide protection against delayed respiratory depression in this setting. 5) There is no indication for the prophylactic use of intravenous nalbuphine in caesarian section patients receiving epidural morphine.

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DATA FROM POST-OPERATIVE CAESARIAN SECTION PATIENTS WHO RECEIVED EPIDURAL MORPHINE

	SALINE N=20	NALBUPHINE N=20
PRURITUS	19	20
PAIN (0-10)	Mean 1.60 ± 2.19	Mean 1.60 ± 1.88
RESPIRATORY RATE < 10	1	1
OXYGEN SATURATION $< 90\%$	1	2

NO RESULTS WERE SIGNIFICANT $p < 0.01$

Title: **PREVENTION OF INTRAOPERATIVE HYPOTHERMIA IN GERIATRIC PATIENTS**

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Introduction: Hypothermia (core T< 36°C) is a common consequence of anesthesia and has been observed more frequently in the elderly [1]. Several methods have been proposed to prevent hypothermia. Among these are: a warm Operating Room, the use of a circulating warm water mattress, humidified and warmed anesthetic gas, reflective blankets, and infrared warmers. Although the warming of infused intravenous fluids should theoretically reduce heat loss, few studies have examined this approach in patients. We studied the effect of heating and humidifying inspired gas, and warming infused intravenous solutions both alone, and together, in a geriatric population. In addition, we monitored subjects in the Recovery Room to assess the effect of hypothermia on recovery from anesthesia.

Methods: After informed consent was obtained, two hundred and twelve patients, aged 65 and over, scheduled for elective surgery under general anesthesia, were studied using a protocol approved by our Institutional Review Board. Patients were randomly assigned to one of four groups:

I. controls: no warming devices used
II. warmed fluids only
III. warmed inspired gas only
IV. warmed fluids and warmed inspired gas

Body temperature was monitored using an external ear canal thermistor probe, Mon-a-therm #503-0013, and a Mon-a-therm model 6500 temperature device, standardized with a mercury thermometer. Infused fluids were warmed using an American Hamilton model DW-1000 fluid warmer with a 3-way stopcock and 84 cm. Pharmaseal K511 extension tubing attached to the fluid warmer tubing. Respiratory gas was warmed and humidified (Conchatherm 3, model 380-80) to an inspired temperature of 37-40°C. No premedication was given. A semi-closed circle absorption system was used with a fresh gas flow of 3 liters per minute. Phenothiazines and butyrophenones were not administered intraoperatively. The remainder of the drug selection was left to the discretion of the attending anesthesiologist. Patient, room, and inspired gas temperatures were measured every 15 minutes; cumulative fluid infused was measured every 30 minutes. Fluid warming was discontinued at the end of the operative procedure. In the Recovery Room, temperature monitoring and a clinical score to assess the recovery from anesthesia, as described by Aldrete and Kroulik [2], were performed every 15 minutes. Criteria for discharge included a clinical score of 8 and a tympanic temperature of 35.6°C (95°F) Statistical analysis of the Operating Room and Recovery Room data was performed using analysis of variance. A p value of ≤ 0.05 was considered significant.

Results: There was no difference among the four groups for age, body surface area, sex, maintenance muscle relaxants, total body surface area exposed during skin prep and surgery, intracavitary vs peripheral procedures, and Operating Room temperature. Of the 200 patients, 184 were in the Operating Room at least one hour and 99 at two hours. After 1 hour, mean temperature had fallen in all groups, with groups III and IV showing significantly less drop than groups I and II. There was no difference between groups I and II and none between III and IV. At the end of 2 hours the results were the same. (Figure). In the Recovery Room, separate analysis of time to reach a score of 8 or 35.6°C indicated no difference among the four groups.

Discussion: It is recognized that moderate hypothermia is a frequent consequence of surgery and anesthesia, and that the elderly are at greater risk for hypothermia. As has been shown before, heating and humidifying inspired gas reduced temperature fall [3]. The use of the fluid warmer, however, was ineffective in reducing heat loss as compared with controls in this study. Although we were able to reduce heat loss in patients when inspired gas was heated and humidified, the effect was not sufficient to hasten recovery from anesthesia or shorten Recovery Room stay.

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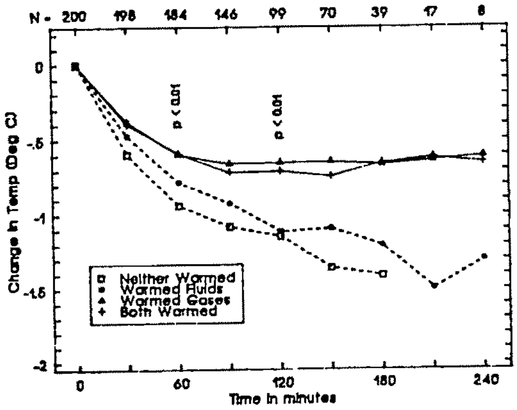

Title: THE INFLUENCE OF HIGH DOSE FENTANYL-DIAZEPAM ANESTHESIA ON CEREBRAL BLOOD FLOW AND CEREBRAL OXYGEN CONSUMPTION

Authors: JM Murkin MD, FRCPC; JK Farrar PhD
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INTRODUCTION

Despite its widespread use during major surgical procedures, very little clinical data exists on the cerebrovascular/metabolic sequelae of high dose fentanyl-diazepam anesthesia. This study was designed to determine the effect of fentanyl-diazepam administration on cerebral blood flow (CBF), and the cerebral metabolic rate for oxygen ($CMRO_2$) in patients undergoing cardiac surgery.

METHODS

Following institutional approval, and after obtaining written informed consent, 12 patients age 55±10 yr (mean±s.d.) undergoing elective coronary artery (n=11) or valvular (n=1) surgery were investigated. Patients were premedicated with 0.10 mg/kg morphine IM, 0.006 mg/kg scopolamine IM, 0.15 mg/kg diazepam PO and their chronic antianginal medications. In addition to radial artery and pulmonary artery catheters, a 15 cm 16 Fr catheter was inserted percutaneously via the right internal jugular vein into the jugular foramen for sampling effluent jugular venous blood, 12 AgCl electrodes affixed to the scalp in a 10-20 bipolar parsagittal montage were used for recording a 10-channel EEG, and 10 scintillation detectors were placed over the cerebral hemipheres. As previously described[1], CBF was determined by the averaged clearance (height/area) of 5-10 mCi ^{133}Xe in 6 ml 0.9% saline and $CMRO_2$ was calculated as the product of the arterial-jugular 0_2 content difference and mean CBF.

After control hemodynamic, CBF, and $CMRO_2$ measurements, anesthesia was induced and maintained with 0.10 mg/kg fentanyl, 0.5 mg/kg diazepam and 0_2. CBF and $CMRO_2$ measurements were repeated 47±6 min following induction of anesthesia. Data were analyzed by paired 2-tailed t-test with significance at $p<0.05$.

RESULTS

Following induction of anesthesia, CBF was reduced from 39±14 to 27±7 ml. 100 gm^{-1} $.min^{-1}$ ($p<0.01$) and $CMRO_2$ from 2.00±0.47 to 1.60±0.27 ml. 100 gm^{-1} $.min^{-1}$ ($p<0.02$) without any significant change in cardiac index (2.33±0.53 $L.m^{-2}$ $.min^{-1}$). $PaC0_2$ was concomitantly reduced from 42±4 to 37±3 mmHg ($p<0.01$) and cerebral perfusion pressure (CPP=MAP-JVP) from 85±12 to 71±9 mmHg ($p<0.01$).

DISCUSSION

This study demonstrates reductions in CBF of 30% and $CMRO_2$ of 20% during high dose fentanyl-diazepam anesthesia. The lower initial values for CBF and $CMRO_2$ ostensibly reflect the effects of the sedative-narcotic premedication[2], while the subsequent reductions result from a further cerebral metabolic suppressant effect of high dose fentanyl-diazepam anesthesia. This is of similar magnitude to that seen following induction of anaesthesia with 0.01 mg/kg fentanyl, 10 mg diazepam and 60% N_20[3]. The similarity between these results, despite a 10-fold variation in fentanyl dosage, presumably reflects the maximal cerebral metabolic suppression achievable with this technique.

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Title: FACULTY BIAS IN RATINGS OF RESIDENT PERFORMANCE

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Introduction. Performance rating evaluations have been found to be important tools for assessing the clinical performance of anesthesia residents, it is commonly observed that these evaluations have good validity, but poor reliability.[1-7] There may be many reasons for the poor reliability of these performance evaluations including a wide range of faculty rating behaviors. We have recently instituted a daily resident evaluation system for anesthesia residents and in this study we report the range of faculty rating behavior in evaluating knowledge and judgement.

Methods. From an initial list of 72 characteristics of a physician, the faculty selected the most important attributes of an anesthesiologist. Seven areas of Knowledge and Judgement (KJ) were identified, as well as, an overall score (Table 1). Each scale was rated as 1 = outstanding; 2 = above average; 3 = average; 4 = marginal or 5 = unsatisfactory.

Table 1

KNOWLEDGE AND JUDGEMENT
1. appropriate medical decisions
2. anticipates preoperative problems
3. anticipates intraoperative problems
4. anticipates postoperative problems
5. thorough knowledge of medicine
6. separates important points from details
7. aware of own limitations

OVERALL KNOWLEDGE AND JUDGEMENT

The study consisted of 14 second year residents and 34 faculty raters. Evaluations were compiled on a daily basis by the faculty. Over the initial seven month period, 865 forms were returned. These were scanned optically, and the information was stored in a computer database. Faculty ratings were examined and extremes of rating means, variance, and form completion were identified.

Results. The mean of the Knowledge and Judgement (MKJ) subscores was 2.67 ± 0.18. Four "hawks" (MKJ less than 2.97) and five "doves" (MKJ greater than 2.29) scored residents one standard deviation above or below the mean of the entire faculty (Fig 1). Seven faculty were identified that gave nearly every resident the same score. The mean standard deviation of scores in these faculty was less than 0.18. Fourteen (41%) faculty remained unassigned to any group (Fig 2).

The Interrater Correlation (IRC) was .478 when all faculty members were included. Exclusion of faculty with low variance, results in a slightly improved IRC. Exclusion of the Hawk/Dove group led to a slightly worse IRC (Table 2).

Table 2

Group	N	IRC
1. All Faculty (no exclusions)	33	.478
2. Hawks/Doves excluded	24	.467
3. Low Variance Group excluded	27	.483
4. Both 2 and 3 excluded	13	.502

Figure I: Average of knowledge and judgement scores by individual faculty

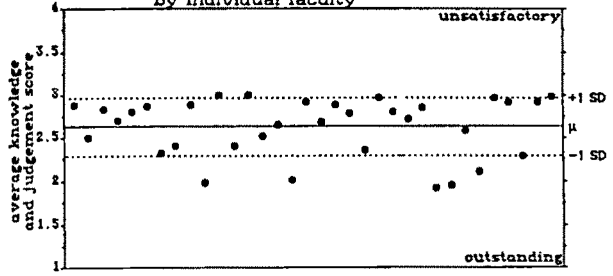
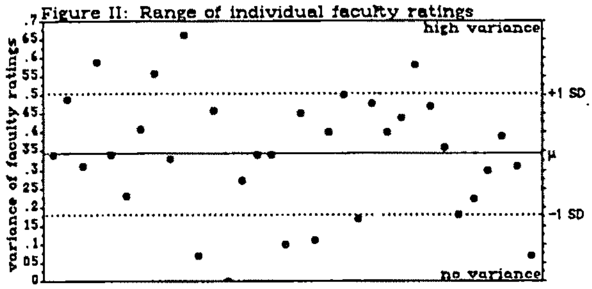


Figure II: Range of individual faculty ratings



Discussion. It has been noted that clinical performance ratings may not be reliable.[2,5-7] Many factors may be responsible for this poor reliability including the wide range of faculty rating behavior, the selection of characteristics to be rated, or an unclear definition of the characteristic to be evaluated. In an effort to determine if differences in faculty rating behavior contribute to low reliability, we selectively excluded the identified faculty rating groups in the computation of test reliability. Exclusion of these groups led to no significant difference in the reliability of test results. For this reason we conclude the range of faculty ratings probably does not effect the overall reliability of the evaluation results.

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Title: ANESTHESIA AND LIVER TOLERANCE TO OXYGEN DEPRIVATION IN PIGS

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Introduction: Different anesthetics can affect oxygen supply–demand relationships and improve or deteriorate tolerance of an organ to oxygen deprivation to different degrees. Surgical outcome of patients suffering from massive hemorrhage and those undergoing any surgery requiring temporary crossclamping of the hepatic vessels or the aorta above the celiac artery depends on the ability to tolerate hepatic ischemia. This study was designed to test the hypothesis that different anesthetics provide different degrees of protection of the liver from hepatic oxygen deprivation.

Methods: The study was approved by the Animal Use Committee. Experiments were performed on 31 minipigs weighing 20-32 kg. The animals were anesthetized with sodium methohexital, 20 mg·kg-1 i.m.; muscle relaxation was achieved with pancuronium, 0.1 mg·kg-1 i.v.; controlled ventilation with equal concentrations of oxygen and nitrous oxide was adjusted to achieve normocarbia. Laparotomy was performed; portal vein dissected and an appropriate size tube with a y-connector was inserted so that blood from the preportal area could be directed through the hepatic end of the portal vein to the liver or through the y-connector to the left jugular vein. Portal blood flow to the liver and hepatic arterial blood flow were measured with an electromagnetic flowmeter using cannulating electromagnetic probes. Constricting clamps were placed on the hepatic artery and portal vein. Nitrous oxide was discontinued at the end of surgical preparation. Hepatic oxygen delivery (DO_2) and consumption ($\dot{V}O_2$) as well as hepatic lactate uptake (L_u) and release of enzymes by the liver were determined during a step-wise reduction of hepatic blood supply under anesthesia with halothane, 1 MAC (Group H–7 pigs), isoflurane, 1 MAC (Group I – 6 pigs), enflurane, 1 MAC (Group E–6 pigs), fentanyl, 100 $\mu g \cdot kg^{-1}$ i.v. followed by an infusion of 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (Group F–7 pigs), or pentobarbital, 30 $\mu g \cdot kg^{-1}$ i.v. followed by 1-2 $mg \cdot kg^{-1} \cdot hr^{-1}$ (Group PB–5 pigs). The step-wise reduction in hepatic blood supply was followed by total occlusion of hepatic artery and portal vein for one hour; then both clamps were completely released and hepatic reperfusion allowed. L_u was determined as follows: $L_u = (C_aL \times HABF + C_{pv}L \times PBF) - C_{hv}L \times (HABF + PBF)$, where L_u = lactate uptake in $mg \cdot min^{-1} \cdot 100g^{-1}$; C_aL, $C_{hv}L$, and $C_{pv}L$ = lactate concentrations in hepatic, arterial, and portal venous blood in $mg \cdot dl^{-1}$, respectively; HABF and PBF = hepatic arterial blood flow and portal blood flow in $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively.

Results: Two animals in Group H, none in Group I, 3 in Group E, 1 in Group F and 1 in Group PB died during the first 15 min of reperfusion. There were no statistically significant differences in the enzyme concentrations in the hepatic venous blood among the groups before induced hepatic oxygen deprivation. After hepatic oxygen deprivation and reperfusion, the enzyme concentrations in the hepatic venous blood substantially (by factors 100-1000) increased in all groups. However, the differences in this increase among the groups did not reach a level of statistical significance. L_u decreased below 1 $mg \cdot min^{-1} \cdot 100g^{-1}$ in all groups of animals except Group I when HABF was completely occluded and PBF was decreased to 25% of baseline values while pigs in Group I maintained L_u even through total occlusion of both hepatic vessels and decreased L_u below 1 $mg \cdot min^{-1} \cdot 100g^{-1}$ for a short period of time only after 15 min of reperfusion. After hepatic oxygen deprivation during reperfusion, hepatic blood flow, DO_2, $\dot{V}O_2$, and L_u recovered to different degrees (Table): during reperfusion, values of hepatic blood flow and DO_2 recovered to 60-70% of baseline values without differences among the groups. Values of $\dot{V}O_2$ during reperfusion recovered also to 60-80% in Groups I,E,F, and PB, and only to 47% in Group H; the differences among the groups, however, did not reach the level of statistical significance. On the other hand, L_u recovered in Groups I,E, and F completely while in Group PB recovered only to 34% and in Group H only to 14% of baseline value ($p < 0.05$).

Discussion: The data suggest that function of the hepatic vasculature and hepatic DO_2 recovered after hepatic ischemic insult during halothane anesthesia faster than cellular hepatic function evaluated by $\dot{V}O_2$ and L_u. To the contrary, somewhat incomplete recovery of function of the hepatic vasculature and hepatic DO_2 was accompanied already by complete recovery of liver function evaluated by L_u. Thus the posed hypothesis is confirmed, at least partially, since the study has demonstrated different degrees of ischemic damage during anesthesia with different drugs. It appears that E, F and, particularly I, provide better protection against hepatic oxygen deprivation and better improvement in tolerance to hepatic oxygen deprivation than PB and, particularly H. The mechanism of such protection remains to be elucidated.

Table

Percent Recovery After Hepatic Ischemic Insult
(Mean ± SE)

	H	I	E	F	PB
L_u	14 ± 15*	116 ± 95	106 ± 59	103 ± 63	34 ± 68
DO_2	59 ± 22	63 ± 37	66 ± 40	66 ± 27	68 ± 24
$\dot{V}O_2$	47 ± 14*	61 ± 13	79 ± 26	75 ± 50	66 ± 14
DO_2-$\dot{V}O_2$	64 ± 36	67 ± 52	115 ± 83	90 ± 65	74 ± 39
$DO_2/\dot{V}O_2$	132 ± 57	106 ± 54	117 ± 22	117 ± 71	104 ± 27

L_u = hepatic lactate uptake, $mg \cdot min^{-1} \cdot 100g^{-1}$; DO_2, $\dot{V}O_2$, $DO_2 - \dot{V}O_2$ = hepatic oxygen delivery, hepatic oxygen uptake and delivery–uptake gradient, respectively $mlO_2 \cdot min^{-1} \cdot 100g^{-1}$; $DO_2/\dot{V}O_2$ = hepatic oxygen delivery/uptake ratio. $^*p < 0.05$ *vs* other groups.

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Title: CHANGES IN CARDIAC OUTPUT DURING ELECTROCONVULSIVE THERAPY

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Introduction. Electroconvulsive therapy (ECT) may provoke profound cardiovascular responses as the result of both electroshock stimulus and the consequent seizure (1). Although initial vagal stimulation may be averted by pre-ECT use of anticholinergic agents, significant sympathetic hyperactivity may follow ECT, resulting in hypertension and tachycardia. The purpose of this study is to investigate changes in cardiac output in the 6 stages during ECT by noninvasive thoracic electrical bioimpedance (TEB) (2).

Methods. Twenty-eight ASA II or III patients scheduled for ECT were studied. This study was approved by the institutional review board. There were 2 male and 26 female patients with mean age of 59 years (ranging 25-82). All patients were premedicated with 0.2 mg of glycopyrrolate. Each patient was monitored with ECG, automated blood pressure measurement, and thoracic electrical bioimpedance (NCCOM3, BoMed). Anesthesia was intravenously induced with methohexital 50-80 mg and succinylcholine 50-80 mg, and ventilation was controlled by mask until spontaneous respiration returned. Cardiac output was continuously measured with TEB (2).

Hemodynamic data such as (1) cardiac output (CO), (2) systolic blood pressure (SBP), and (3) heart rate (HR) were documented in the following stages: Stage 1, preinduction; Stage 2, anesthesia induction; Stage 3, ECT shock; Stage 4, seizure; Stage 5, post-seizure; and Stage 6, awake. Data were analyzed by modified t-test and $p < 0.01$ was considered statistically significant.

Results. The mean values of those data are listed in the table. CO: There were statistically significant increases in mean CO with ECT shock (8.7 L/min) and seizure (8.8 L/min) compared with preinduction CO (6.7 L/min; $p < 0.01$). CO in the post-seizure stage had a tendency to be higher than preinduction CO ($p = 0.06$). However, the amount of energy used for ECT shock (Joules) and the duration of seizure (seconds) had no statistically significant influence in CO.
SBP: There were also statistically significant increases in mean SBP during ECT shock (140 mmHg), during seizure (152 mmHg), and during post-ECT stage (150 mmHg) compared with preinduction SBP (129 mmHg; $p < 0.01$). There was a trend to increase SBP with seizure than with ECT shock ($p = 0.019$). HR: Significant increase in mean HR during ECT shock, seizure, post-seizure, and awake stages ($p < 0.01$). Mean HR also increased from 89/min of preinduction to 100/min with induction of anesthesia ($p = 0.017$).

Discussion. ECT is a commonly used treatment of depressive states and is considered safe with skilled anesthesia (1). Our study demonstrated that ECT shock stimulus and the subsequent seizure significantly increased CO (31%), SBP (18%), and HR (30%) ($p < 0.01$). CO eventually returned to the baseline (preinduction level), although increases in SBP and HR sustained ($p < 0.01$). HR tended to increase with the induction of anesthesia ($p = 0.017$). We conclude that significant hemodynamic changes occur during ECT. These may be detrimental to patients with ischemic and rheumatic heart diseases and, therefore, those patients should be carefully treated during ECT (3).

HEMODYNAMIC DATA

Stages	1	2	3	4	5	6
CO (L/min)	6.7± 2.2	6.2± 2.8	8.7± 2.1	8.8± 2.5	7.6± 1.2	6.6± 1.0
SBP (mmHg)	129 ±12	125 ±25	140 ±13	152 ±13	150 ±16	142 ±23
HR (beats/min)	89 ±14	100 ±11	106 ±10	104 ±12	110 ±11	116 ±13

Values are mean ± SD

$p < 0.01$ in relation to preinduction stage (1)

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Title: INCIDENCE OF POSTOPERATIVE HYPOXEMIA IN THE RECOVERY ROOM DETECTED BY THE PULSE OXIMETER

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Introduction. Hypoxemia has been a matter of concern not only in the operating room (1) but also in the immediate postoperative period (2). However, clinical assessment of postoperative hypoxemia is rather difficult and cyanosis is only detectable when the arterial oxygen saturation (SaO_2) is below 80%. The recent introduction of pulse oximetry has provided a continuous, noninvasive, real-time method to detect SaO_2 intraoperatively and postoperatively. We examined the incidence and risk factors of postoperative hypoxemia in the recovery room by continuously monitoring postsurgical patients with a finger pulse oximeter.

Methods. Following approval from the institutional review board, 101 postsurgical patients were studied consecutively. Each patient was monitored with a finger pulse oximeter (Nellcor Corp) to continuously monitor SaO_2 during the entire recovery room stay by the staff recovery room nurses, and all patients were subsequently evaluated by anesthesiologists. The degree of SaO_2 was categorized into (1) normal (>90%), (2) moderate hypoxemia (<90%, >85%), and (3) severe hypoxemia (<85%).

The association of the following potential risk factors for postoperative hypoxemia was evaluated: age, ASA status, surgical site, body habits, history of asthma, presence of chronic obstructive lung disease (COPD), restrictive lung disease (RLD) and heart disease, smoking habit, anesthesia technique, use of muscle relaxant, reversal of muscle relaxant, airway status, ventilatory status, body temperature, position in the recovery room, supplemental O_2 inhalation, and postanesthesia (PACU) medication. Weight greater than 120% of ideal body habitus was considered as obese.

Results. Of 101 postsurgical patients, 12 patients (11.9%) developed moderate hypoxemia (SaO_2 <90%, >85%) and 6 patients (5.9%) suffered severe hypoxemia (SaO_2 <85%). Smoking habit was significantly associated with postoperative hypoxemia ($p < 0.05$). Supplemental O_2 inhalation decreased the incidence of hypoxemia significantly ($p < 0.05$). There was a trend toward a higher incidence of postoperative hypoxemia in patients with ASA III, chest surgery, and ventilator support.

Supine head-down position and lateral position in the recovery room seemed to have higher incidence of hypoxemia. Age, anesthesia technique, use of muscle relaxant, body temperature, postanesthesia medication, obesity, history of asthma, COPD, RLD, and heart disease had no significant effect on hypoxemia.

Discussion. Arterial hypoxemia is a common but often underdiagnosed phenomenon in the immediate postoperative period during transport to the recovery room and in the recovery room stay (2).

This study demonstrated that smoking habit had a statistically significant effect on postoperative hypoxemia and supplemental O_2 inhalation greatly reduced the risk of hypoxemia. Although statistically no highly significant, the incidence of postoperative hypoxemia had a trend to increase with site of surgery (chest), ventilatory support, supine head-down position, and lateral position. There was no significant difference in the incidence of hypoxemia with obesity, anesthetic technique, asthma, COPD, heart disease, body temperature, and postanesthesia medication.

In conclusion, we recommend that all postsurgical patients should have supplemental O_2 inhalation with preferably supine head-up or flat position.

Total Number = 101

O_2 Saturation	>90% Subtotal (89)	<90%, >85% Subtotal (12)	< 85% Subtotal (6)
Age 1-19 years	12	2	2
20-35 years	11	2	0
35-54 years	28	3	3
55 years	38	5	1
ASA I	15	1	0
II	58	6	4
III*	16	5	2
IV	0	0	0
Surgical site			
Chest*	12	5	2
Upper abd	8	1	0
Lower abd	24	2	1
Peripheral	45	4	3
Smoking Yes+	36	10	4
No	53	2	2
Ventilation status			
Vent*	7	3	1
Spontaneous	82	9	5
Position			
Supine	32	2	0
Lateral*	6	2	2
Supine head-up	48	6	2
Supine head-down*	3	2	2
O_2 inhalation			
Yes	81	8	4
No+	8	4	2

+$p < 0.05$ and *$p < 0.1$

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Title: **THE METHOD OF PRELOAD ALTERATION DOES NOT AFFECT THE SYSTOLIC PRESSURE-VOLUME RELATION IN THE LEFT VENTRICLE IN MAN**

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Introduction. The peak-systolic pressure end-ejection volume relation (PPEVR) has been used to measure left ventricular (LV) function in patients undergoing coronary artery bypass surgery[1]. In this study, changes in volume and pressure were generated by increasing venous blood return to the heart through rapid transfusion into the venous circulation. However, in the original studies of the pressure-volume relation, changes in preload were achieved by decreasing the venous return to the heart[2]. The present study compares PPEVR relations derived in man, using two opposing methods of preload alteration: increasing and decreasing venous blood return to the heart.

Methods. After institutional approval and written informed consent, 6 patients with good LV function were studied during coronary artery bypass surgey. Anesthesia was induced and maintained with fentanyl 50 ug/kg, pancuronium 0.15 mg/kg and 100% oxygen. PPEVR were derived either prior to or after cardiopulmonary bypass while the venous and arterial cannulae were in place. Synchronized continuous recordings of radial arterial pressure by arterial cannula and LV cavity short axis (SA) by 2D echocardiography were obtained. In each measurement, 200 to 800 cc of volume were removed and then returned within 30 to 60 seconds to the venous circulation using the venous cannula. Six or more cardiac cycles were analyzed for each preload alteration. End-ejection volume (EEV) was calculated from the smallest short axis area of the LV as the average of 3 measurements using the formula:

$$EEV = SA^{3/2}(SA+36)/(SA+12).$$

EEV were correlated with peak-systolic pressures (PP) of the same cardiac cycles according to the relation $PP = E \times (EEV - V_0)$ using least squares linear regression. The slope E which relates EEV and PP represents contractility. For each patient, E values obtained by increases and decreases in preload were compared. The statistical significance of the measured differences was assessed using a modification of the Student's T-test for linear regressions. $P < .05$ was considered statistically significant.

Results. 8 pairs of PPEVR were determined in 6 patients. The E values determined by augmenting venous return were 4.0 ± 4.8 (mean ± SD) while those determined by diminishing venous return were 3.44 ± 4.0 . Of the 8 pairs of PPEVR, 6 showed no difference regarding the manner in which they were obtained (positive vs. negative preload alteration). For one pair, the slope obtained by positive preload alteration was significantly larger than that obtained with the negative maneuver while for another pair the opposite was true. Both these studies however were of poorer technical quality than the others. In one case the LV appeared to be never adequately filled by echocardiographic criteria while, in the other, the LV endocardium was difficult to visualize.

Discussion The PPEVR has been shown to be a good measure of LV contractility. Since in previous investigations both augmentation and diminution of LV preload have been used, this study was undertaken to determine how these two methods compare. Our findings, that for the majority of the measurements no statistically significant differences in slopes of the PPEVR were observed, suggest that the preload alterations by which these relations are generated are not important. It may therefore be possible to determine LV contractility using the PPEVR in a manner which is best suited or safest considering each patients preload status.

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Title: PROTECTION OF ISOLATED RAT HEPATOCYTES FROM THE ATTACK BY ATRACURIUM METABOLITES IN VITRO

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Spontaneous degradation of atracurium at pH 7.4 and 37°C (the so called Hofmann elimination, HE), was postulated to contribute significantly to the inactivation and degradation of atracurium.[1,2] If the reaction occurs at both sites susceptible to HE, two acrylate groups may be formed from one molecule of atracurium. Due to their electrophilic character, acrylates formed in vivo may bind to endogenous nucleophiles. This reaction may have undesired consequences if the alkylation reaction involves nucleophiles responsible for the maintenance of the functional and/or structural integrity of the cells. We tested the working hypothesis that the cytotoxic effect of acrylates may be reduced or eliminated if, in a reaction with a nucleophile, acrylates were converted to inactive acrylate-nucleophile adducts prior to their addition to isolated hepatocytes.

Extrusion of lactic dehydrogenase (LDH) from isolated liver cells into the culture medium was used as a quantitative estimate of disruption of cellular membranes. Isolated hepatocytes were obtained from rats anesthetized with pentobarbital (60 mg/kg ip)[3,4] and incubated for 4 h with: 1) atracurium (0 to 800 μM), 2) its degradation products formed by allowing the spontaneous degradation to proceed for 180 min (in the cell incubation medium at pH 7.4 and 37°C) prior to the addition of the medium to the hepatocytes, and 3) the adducts of metabolites and cysteine. The adducts were formed by admixing a molar surplus of ℓ-cysteine to the products of atracurium degradation at the start of the third hour of the 3 h period allowed for the spontaneous degradation. LDH was measured spectrophotometrically in the cell-free incubation medium at the end of the 4 h incubation period. Each concentration of atracurium under each condition was tested in three culture dishes (a total of 48 dishes) containing hepatocytes from a single animal. The experiment was repeated with 6 rats.

Extrusion of LDH from cells exposed neither to atracurium nor to its degradation products amounted to less than 10% of the total intracellular content of the enzyme. The presence of ℓ-cysteine (3mM) did not change this value in the absence of atracurium or its metabolites. Extrusion of LDH into the culture medium from cells exposed to atracurium was directly related to the concentration of atracurium initially added to the incubation medium. When the same concentrations of atracurium were allowed to degrade spontaneously prior to the addition to the hepatocytes, the extrusion of LDH was markedly increased. Admixture of cysteine to the degradation products, prior to the addition to the hepatocytes, completely prevented the extrusion of LDH that was observed with the degradation products alone.

The results confirmed the working hypothesis that the products of the spontaneous degradation of atracurium display cytotoxic properties. Whether the cytotoxicity observed on addition of atracurium to the hepatocytes is due to the toxicity of the parent drug or to that of the products formed via HE during the incubation of atracurium with hepatocytes cannot be presently resolved. Since the admixture of cysteine completely abolished the cytotoxic effect of atracurium metabolites, it seems plausible to postulate that the metabolites are electrophilic acrylates which, by alkylating nucleophiles in the cellular membranes, produce cell lysis. Antecedent covalent binding of acrylates to cysteine satiated the reactivity of acrylates and preserved the nucleophiles in or on the cells and, hence, the cellular integrity.

We conclude that atracurium belongs to the group of drugs with electrophilic metabolites which can alkylate endogenous nucleophiles.

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Acknowledgement

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TITLE: DOES THE CHOICE OF CRYSTALLOID AFFECT MATERNAL AND NEONATAL GLUCOSE HOMEOSTASIS AT CESAREAN SECTION?

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INTRODUCTION. Infusion of large volumes of normal saline (NS) but not plasmalyte (PL) during cesarean delivery can acutely lower maternal pH and increase the incidence of neonatal acidosis[1]. However, PL contains acetate and gluconate which may upset maternal and fetal carbohydrate metabolism and risk neonatal hypoglycemia[2]. In this study, we compared the effects of hydration with NS or PL on maternal and neonatal glucose (G) homeostasis.

METHODS. 20 ASA I and II term parturients scheduled for elective cesarean section under spinal anesthesia gave written, informed consent and participated in this institutional review board approved protocol. All fasted at least 8h before anesthesia and surgery and none suffered any known abnormality of G metabolism. In a random manner, we administered either NS (n=10) or PL (n=10) during surgery and the first 2h of recovery. Using a reflectance photometer (Accuchek II^R, Biodynamics, Indianapolis, IN), we measured maternal blood G concentration before administering IV fluids, at delivery and 2h postpartum. We determined neonatal blood G concentration in umbilical artery blood obtained at delivery, and in a capillary blood sample at 1,2, and 4h after birth. If a mother or infant received intravenous or oral glucose containing fluids during the study, we did not obtain subsequent blood samples. Using Student's t-test, we analyzed our data to determine the significance ($p<0.05$) of any differences in measured values. All data are mean ± SD.

RESULTS. Patients in both groups were similar in age, height, and weight. Both groups also had comparable induction-to-delivery and uterine incision-to-delivery intervals and they received nearly identical volumes of fluid both before induction of anesthesia and by the time of delivery. Maternal blood G concentrations were similar in both groups (Fig.1). Maternal blood glucose concentration increased from 80.5 ± 13.1 (SD) mg/dl before anesthesia to 101.4 ± 20.3 mg/dl ($p<0.0001$) at delivery and then decreased to 85.6± 21.3 mg/dl by 2h postpartum ($p<0.05$ vs delivery). One woman, who was asymptomatic, had a baseline blood glucose below 60 mg/dl (45 mg/dl). Her blood glucose concentration increased to 48 mg/dl at delivery and to 58 mg/dl by 2h postpartum. Neonates in both groups had similar blood glucose concentrations throughout the study (Fig.2). Mean neonatal blood glucose concentration measured 48.2 ± 9.7 mg/dl in umbilical artery blood, and remained stable during the study period. 7 infants received glucose for various reasons during the study period. Only 3, 2 in the NS group and 1 in the P group developed significant hypoglycemia (BS<30 mg/dl).

DISCUSSION. Acetate can inhibit cellular G uptake and metabolism[3] and gluconate may be converted to G[2]. However, we found that infusion of these compounds in PL for hydration during cesarean section does not alter maternal or neonatal G homeostasis. Nonetheless, occasional infants in each group required treatment for hypoglycemia. Thus, although a glucose free fluid regimen decreases the risk of neonatal hypoglycemia[4], this potentially dangerous condition may still develop.

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Figure 1.

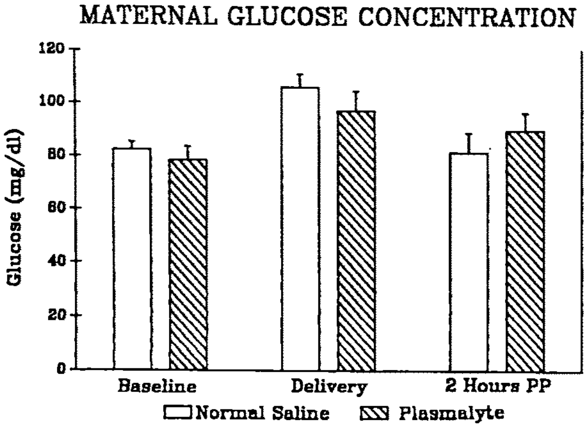
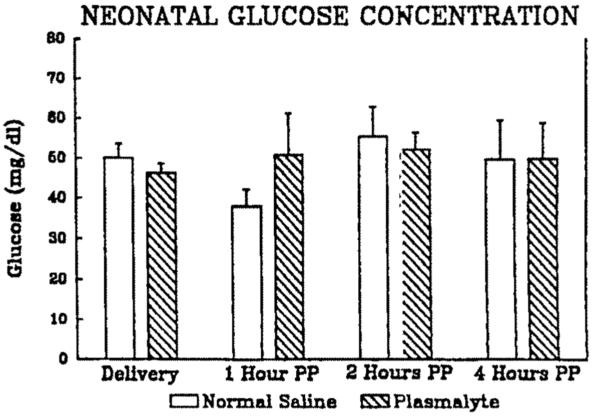


Figure 2.



TITLE: A STUDY OF DENITROGENATION DURING PREGNANCY

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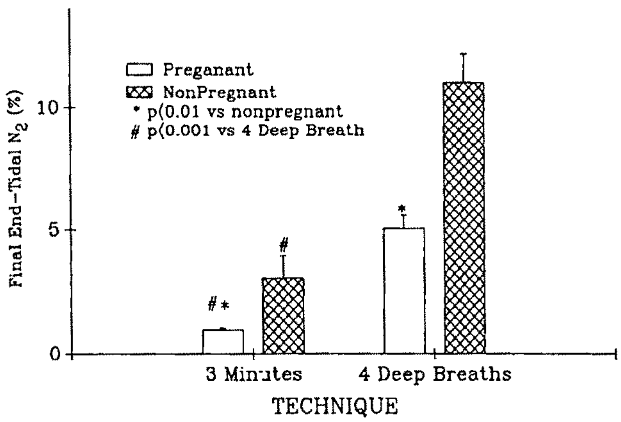
Introduction. Denitrogenation with 100% O_2 is a crucial part of the rapid sequence induction which precedes a general anesthetic in parturients. However, the technique used and the time required for optimal denitrogenation are still uncertain. We designed this protocol to study, by measuring nitrogen washout, the efficacy of two commonly used methods of pre-oxygenation: three minutes tidal breathing of 100% O_2 and four deep breaths of 100% O_2 within 30 seconds. For comparison, we also studied non-pregnant volunteers.

Methods. Ten healthy parturients (18-40 wks gestation) and six non-pregnant females of reproductive age gave written informed consent to participate in this institutional review board approved study. While quietly lying supine, the subjects breathed 100% O_2 at a fresh gas flow of 8 l/min through a tight-fitting face mask and a circle anesthesia system. A Nitralyzer 505^R (Med Science, St. Louis, MO) with a needle valve placed at the elbow of the breathing system continuously measured N_2 concentration. In random order, each subject participated in 2 trials: 3 minutes tidal breathing and 4 deep inspirations within 30 seconds. Before each trial, we calibrated the nitrogen analyzer with 0%, 30% and 79% N_2 and then flushed the circuit with 100% O_2. For the 4 deep breath trials, the subjects were instructed to "take a deep breath, all the way in, and blow it all the way out" 4 times. The volunteers breathed room air for at least 10 minutes between trials.

We used analysis of variance for repeated measures to compare denitrogenation between the techniques and the two groups of women and considered $p<0.05$ significant.

Results. Three of the 10 parturients smoked cigarettes while none of the non-pregnant women smoked. The figure shows the results of the denitrogenation studies. The non-pregnant volunteers required 117.0 ± 33.0 s (mean ± SD) to achieve 5% end-tidal N_2 while parturients required only 54.5 ± 24.9 s ($p<0.001$).



Discussion. Standard obstetrical anesthesia texts[1] recommend pre-oxygenation for 3 minutes or 4 deep breaths of 100% O_2 before induction of general anesthesia in parturients. These recommendations are based on data from non-pregnant patients showing that breathing 100% O_2 for 3 minutes at fresh gas flow rates of at least 4-5 l/min achieves adequate denitrogenation (end tidal N_2 $\leq 5\%$)[2] and a more recent study showing that both 3 minutes of tidal breathing and 4 deep breaths of 100% O_2 within 30 seconds produce similar increases in P_aO_2 in parturients during induction of anesthesia for cesarean section[3]. Recently, Russell et al[4], using a Magill breathing system, demonstrated significantly faster pre-oxygenation in parturients as compared to non-pregnant women. However, they found no significant improvement in the rate of pre-oxygenation when comparing tidal and vital capacity breathing. Our results agree in part with theirs. Using a circle anesthesia system, parturients denitrogenate markedly faster than do non-pregnant women. This markedly shortened time to 5% end-tidal N_2 suggests that 95% of parturients should denitrogenate adequately within 2 minutes (mean +2 SD) and do not require a full 3 minutes for pre-oxygenation.

Pregnancy-induced changes in the respiratory system probably account for the rapidity of denitrogenation in these women. Pregnancy decreases FRC by 20-25%, decreasing the amount of N_2 stored in the lungs. In addition, tidal volume, respiratory rate and minute ventilation all increase, augmenting the rate of N_2 washout.

We were not plagued, as Russell et al[3] were, by mask leaks when performing the 4 deep breath technique and we found that adequate denitrogenation does occur in pregnant women after 4 deep breaths within 30 seconds.

In conclusion, in parturients, either 2 minutes of tidal breathing or 4 deep breaths within 30 seconds of 100% O_2 should provide adequate denitrogenation prior to induction of general anesthesia.

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Title: SEDATIVE EFFECTS AND RECOVERY AFTER DIFFERENT DOSES OF INTRAVENOUS MIDAZOLAM AND DIAZEPAM

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Introduction. Midazolam is frequently used as an intravenous sedative because of its short elimination half life. However, during the past two years, the FDA has received 57 reports of severe cardiovascular or respiratory events which included 30 deaths and 4 cases of hypoxic encephalopathy (D.L.Skelly, personal communication). The potency of midazolam has been estimated to be about 2:1 over diazepam (1), but recent evidence indicate that the potency of midazolam has been underestimated (2) and much smaller doses should be used. We conducted the following study to further evaluate the dose relationship between midazolam and diazepam.

Methods. Eleven healthy male volunteers (23.1 ± 4.7 yr, 68.7 ± 10.2 kg, 174.0 ± 7.2 cm) participated in a double-blind, randomized, placebo-controlled, cross-over trial. This study was approved by our institutional clinical investigation committee and written consent was obtained from each subject. The subjects were studied 6 times successively with a one-week wash-out period between the treatments. Each test day the subjects randomly received by slow intravenous injection either saline placebo, midazolam (0.05, 0.1 or 0.15 mg/kg) or diazepam (0.15 or 0.3 mg/kg). The depth of sedation was estimated at 5, 10, 15, 20, 30, 40 and 50 minutes after injection by using a scale: 1=awake (resting with eyes open); 2=asleep, easily arousable (opened eyes and responded after the subjects name was called twice); 3=asleep, difficult to arouse (responded only after the subjects name was loudly called and after being shaken from the shoulders); 4=asleep not arousable (did not respond to a loud voice and shaking). Before and one hour after the injection, the central nervous system depressant effect was studied by measuring the auditive simple reaction time of the subjects: the subjects pressed the space-bar on a computer keyboard after hearing a sound. The score recorded is the average of a series of 10 reactions.

Results. The mean scores of sedation are presented in Fig. 1. The strongest effect was seen after the highest dose of midazolam and the mildest after the small dose of diazepam. Within the first 10 minutes after injection the sedative effects of the high dose of diazepam (0.3 mg/kg) were between the effects of the two smallest doses of midazolam (0.05 and 0.1 mg/kg), indicating a dose ratio of approximately 5:1.

The mean reaction times are presented in Fig. 2. At baseline, one hour before injection, no significant differences between treatment groups were seen. One hour after injection, the drug-induced increases in reaction times were highly significant ($p<0.0001$, one-way analysis of variance for repeated measures). The reaction times after the two highest doses of midazolam were significantly longer than those seen after placebo or the lowest doses of diazepam and midazolam ($p<0.05$, Fischer PLSD test). The difference in reaction times was also significant between the highest dose of midazolam and the highest dose of diazepam. The dose ratio here is approximately 6:1.

Discussion. The results clearly indicate that, in the dose range used, the ratio of equipotent doses of diazepam and midazolam is closer to 5:1 or even 6:1 rather than 2:1 as earlier suggested. The recovery after midazolam sedation has been estimated to be longer than expected in relation to its short half life of elimination (3). It is possible that by using smaller doses of midazolam adequate sedation with a greater safety and a faster recovery could be achieved.

Fig. 1

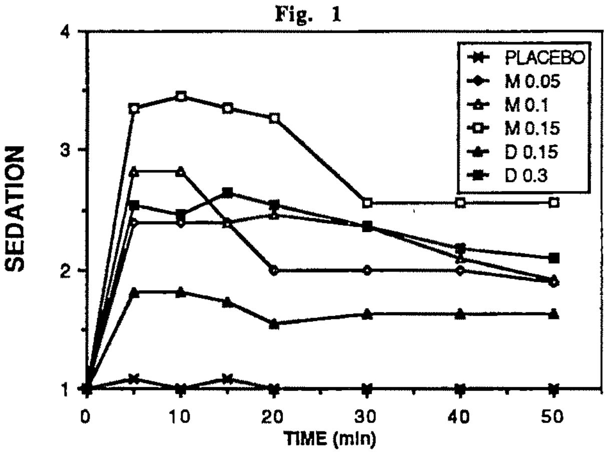
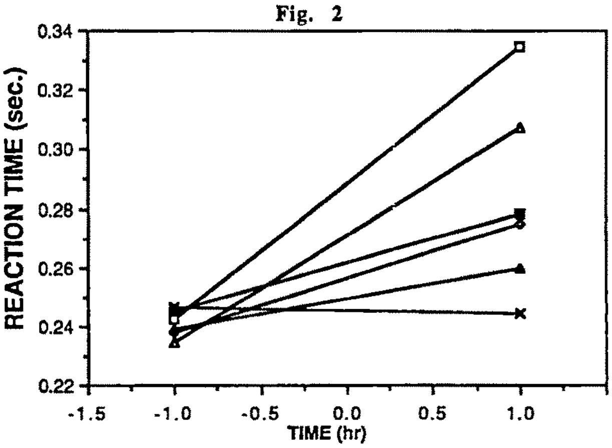


Fig. 2



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Title: THE ANTINOCICEPTIVE ROLE OF MU AND DELTA OPIATE RECEPTORS AND THEIR INTERACTIONS IN THE SPINAL DORSAL HORN OF CATS

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Introduction. Clinical studies and animal behavior have demonstrated that the intrathecal or epidural administration of opiates can produce a reduction in pain ratings or response to noxious stimuli. However, the role of the different subtypes of opiate receptors in the control of pain at the level of the spinal cord still remains controversial. An important tool in pharmacology when one wants to avoid side effects is to use low doses of several agents that produce the same effect. This study is part of a series of experiments aimed at determining the optimum drug combination that could be used to produce maximal depression of noxiously evoked activity at the level of the spinal cord, while at the same time reducing the total amount of any one agent and, therefore, the likelihood of side affects associated with any particular drug.

Methods. This protocol was approved by the Yale University Animal Care and Use Committee. Extracellular single unit activity was recorded from single spinal dorsal horn neurons in decerebrate spinal cord transected cats. Surgical preparation which included tracheostomy and external jugular vein and carotid artery cannulation were carried out under general anesthesia (halothene/nitrous oxide/oxygen). Following animal instrumentation, cats were rendered decerebrate by electrolytic lesions in the midbrain reticular formation and the spinal cord was transected at T-12. Anesthesia was discontinued following decerebration. Tungsten microelectrodes were advanced into the lumbar spinal dorsal horn which had been exposed by an L4-6 laminectomy. Neuronal activity was recorded from single discriminated wide dynamic range (WDR) neurons. Noxiously evoked activity was produced by a 51°C, 8 sec radiant heat stimulus focused on the most sensitive area of the neurons' receptive field. Following control studies, drug in normal saline was applied gently onto the spinal cord. Drugs consisted of 1, 1.5, 10 and 20 ug of DAGO (mu selective opiate agonist) or 25, 100, and 250 ug of morphine sulfate (non-selective mu agonist), or 30, 100, and 200 ug of DPDPE (delta selective agonist). Combination studies involved the administration of either 1 or 1.5 ug DAGO, with 30 ug of DPDPE.

Results. Data were obtained from 82 neurons. Only 1 cell was studied in each animal. Spinally administered DAGO, morphine, and DPDPE showed dose-dependent suppression of the noxiously evoked activity of WDR neurons. The dose-response relationship of DAGO, morphine, and DPDPE showed good linear correlation, and the ED50 for these drugs were determined to be 5.1, 124.9, and 159.9 ug respectively. As shown in Figure 1, the 1 ug dose of DAGO and the 30 ug dose of DPDPE produced no significant suppression of the noxiously evoked activity. However, the combination of those two subanalgesic doses produced a supra-additive effect resulting in suppression equal to 23%. DAGO 1.5 ug by itself was capable of producing significant suppression and, when combined with DPDPE (30 ug) produced an even greater, again supra-additive suppression of noxiously evoked activity.

Discussion. The present study shows that there is a dose-response relationship associated with the suppression of noxiously evoked activity of WDR neurons by the spinal administration of DAGO, morphine, and DPDPE. In addition, the combination studies demonstrate that when subanalgesic doses of either a mu or delta agonist are combined, a supra-additive interaction can be produced resulting in significant suppression of noxiously evoked activity. These findings suggest that drug combinations which include both mu and delta selective agonists may be an appropriate way of lowering the total amount of any one drug in the spinal cord. And, thus, decreasing the likelihood of side effects, while at the same time producing significant analgesia.

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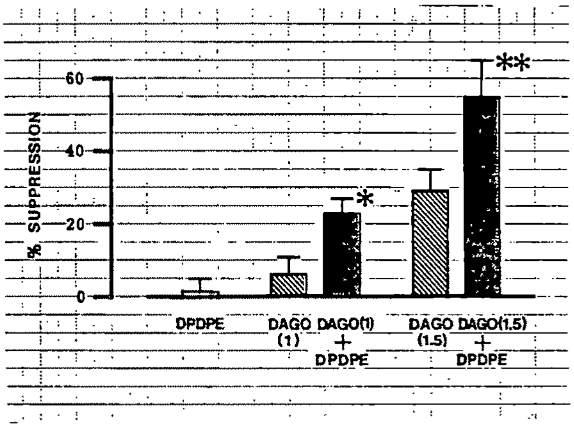

Fig. 1. Interaction of DAGO (1 or 1.5 ug) and DPDPE (30 ug) *, ** $p<0.05$ compared with DAGO 1 or 1.5 ug.

Title: SPINAL DELTA BUT NOT MU OPIATE RECEPTORS APPEAR TO INTERACT WITH NORADRENERGIC SYSTEMS IN THE CAT'S SPINAL DORSAL HORN

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Introduction. The complex pharmacology associated with spinal modulation of pain information has provided a wealth of potential regimes for pain management. Recently, several studies have demonstrated synergistic antinociception following low-dose administration of opiates and alpha-2 adrenergic agonists at the spinal level. These synergistic effects could be extremely important as a tool by which adequate spinal analgesia could be produced by the administration of several different substances at minimal dose, thus avoiding the potential side effects associated with any one individual agent. As such, this study was carried out in order to define the subtypes of opiate and noradrenergic receptors that are likely to be involved in synergistic antinociception that has been seen when those systems have been combined at the level of the spinal cord. We examined, using a sensitive neurophysiologic assay, possible interactions between the selective mu agonist DAGO, the nonselective mu agonist, morphine or the selective delta agonist DPDPE when combined with clonidine.

Methods. This protocol was approved by the Yale University Animal Care and Use Committee. Surgical preparation which included a tracheostomy and jugular vein and carodid artery catheterization was performed under general anesthesia (halothane/nitrous oxide/oxygen). Following decerebration by electrolytic lesions in the mid-brain reticular formation anesthesia was discontinued. The spinal cord was transected at T-12 in order to remove all supraspinal effects. Tungsten microelectrodes were advanced into the lumbar enlargement of the dorsal horn of the spinal cord which had been exposed by a laminectomy (L4-6). The extracellular neuronal activity was recorded from discriminated single wide dynamic range (WDR) neurons. Noxiously evoked activity was produced by the presentation of a 51°C radiant heat stimulus (8 sec) to the cell's receptive field in the periphery. Following control studies, the drugs, in normal saline, (0.5 ml, 37°C) were applied gently onto the spinal cord. Drugs consisted of either 1 or 1.5 ug DAGO, 25 ug morphine or 30 ug DPDPE. In combination, each drug described above was combined with 5 ug of clonidine.

Results. As shown in Fig. 1, 1 ug of DAGO, 25 ug of morphine, 30 ug of DPDPE, or 5 ug of clonidine all produced no statistically significant suppression of WDR neuronal activity. 1.5 ug of DAGO showed a slight, but significant suppression. The combination of the ineffective dose of morphine or DPDPE with clonidine produced a synergistic suppression (49% or 54%, respectively). However, a combination of low-dose clonidine with either the ineffective or the slightly effective dose of DAGO (1 and 1.5 ug) failed to produce any synergistic antinociceptive effect.

Discussion. The pharmacology of spinal pain modulation appears to be extremely complex. That complexity provides important potential new ways to treat both accute and chronic pain. The purpose of this study was to try to determine the best combination of known opiate and alpha-2 adrenergic receptor agonists that at the lowest possible dose could produce significant suppression of noxiously evoked activity. In this study, both the delta selective agonist DPDPE and the non-selective mu agonist morphine were capable of producing a synergistic suppression when combined with clonidine. However the combination of both an ineffective and slightly effective dose of the selective mu agonist DAGO when combined with clonidine showed no similar synergistic effect. These results would suggest that opiate agonists with delta receptor affinity may be more appropriately combined with alpha-2 agonists in order to produce a synergistic effect in blocking spinal pain transmission. Recent reports that morphine spinal antinociception may be mediated at delta receptors (1,2) are in agreement with the results of the present study.

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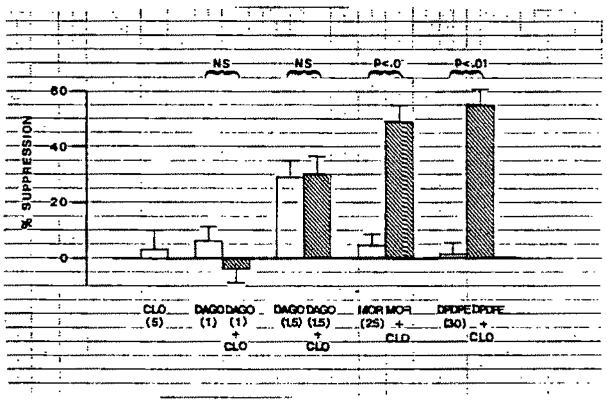

Fig. 1. The effect of DAGO (1 or 1.5ug), Morphine (25ug), or DPDPE (30 ug), alone or combined with clonidine (5 ug).

Title: **LEFT VENTRICULAR FUNCTION DURING AORTIC ANEURYSM RESECTION: THE INFLUENCE OF ANESTHETIC TECHNIQUE.**

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Dublin, Ireland.

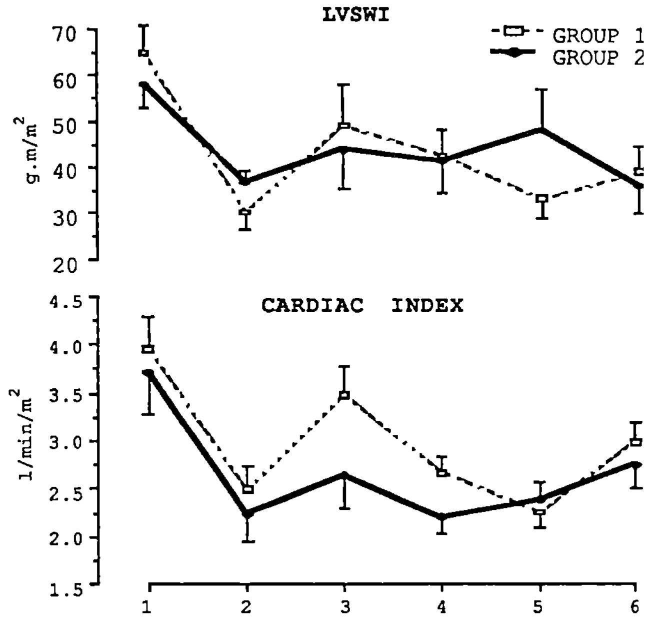
INTRODUCTION The high prevalence of coexisting ischemic heart disease in patients presenting for abdominal aortic aneurysm resection is well documented and myocardial infarction is responsible for 40-70% of the reported perioperative mortality[1]. Limited data is available on the influence of anesthetic technique on cardiac performance during aortic vascular surgery. "Balanced" nitrous oxide/ oxygen/opiate and a nitrous oxide/oxygen/volatile agent techniques[2,3] have been associated with a depressed left ventricular performance during induction of anesthesia, which persisted during aortic cross clamp application. High dose fentanyl (100 µg/kg)/oxygen technique has been associated with an unacceptably high incidence of hyperdynamic circulatory changes prior to, during, and following cross clamping.[4]

The objectives of this study were to compare the hemodynamic changes associated with high dose fentanyl/oxygen/isoflurane anesthetic technique with a nitrous oxide/oxygen/isoflurane/ low dose fentanyl technique for elective aortic aneurysm resection.

METHODS Following institutional Ethics Committee approval and informed consent 19 consecutive patients (ASA II to III) were prospectively evaluated during a one year period. Group I (n=10) were given thiopental 4 mg/kg for induction of anesthesia and nitrous oxide/oxygen/isoflurane 0.5-1% with low dose fentanyl for maintenance of anesthesia. Group II (n=9) received fentanyl 30 µg/kg for induction of anesthesia followed by fentanyl infusion (20 µg/kg/hr)/ isoflurane 0.2-0.5% for maintenance of anesthesia. Preoperative LVEF was determined by radionuclide scanning. Patients were premedicated with diazepam 0.15 mg/kg orally 90 minutes prior to surgery. Radial and pulmonary artery catheters were placed with local anesthesia and 3-6 µg.kg fentanyl sedation. Vecuronium priming dose (0.02 mg/kg) followed by 0.1 mg/kg was used to facilitate tracheal intubation and controlled normocapnic ventilation was employed. Standard CM5 ECG monitoring was utilised to detect intraoperative dysrhythmias and myocardial ischemia. PCWP was maintained between 10-15 mmHg and hypertension > 20% baseline was controlled by nitroglycerin infusion. Measured and derived hemodynamic data was obtained 3 minutes before and after induction of anesthesia, aortic cross clamping and release. Statistical analysis included multivariate analysis of variance (MANOVA) and Mann-Whitney U testing. Data was expressed as mean ± SEM. $P<0.05$ was considered significant.

RESULTS The two groups were similar with regard to age, history of previous myocardial infarction and preoperative LVEF. The changes in cardiac index and left ventricular stroke work index before and after induction of anesthesia, aortic cross clamp and aortic cross clamp release are illustrated in Figures 1 and 2. Both groups were associated with significant reductions in cardiac index and LVSWI on induction of anesthesia. There was no significant difference between the two groups during or following cross clamping and release. PCWP was similar in the two groups. No ECG evidence of myocardial ischemia was detected.

FIGURE 1



1 = Baseline
2 = Steady state anesthesia
3 = Pre-clamp
4 = Post-clamp
5 = Pre-unclamp
6 = Post-unclamp

DISCUSSION A combined high dose fentanyl/oxygen/ isoflurane anesthetic technique was not associated with a significantly improved left ventricular performance compared with a conventional nitrous oxide/oxygen/isoflurane/low dose fentanyl technique. However, the combined opiate/oxygen/ volatile agent technique maintained a stable CI, LVSWI and SVR during the cross clamp period and was not associated with hyperdynamic circulatory responses previously reported with unsupplemented fentanyl/oxygen technique[4]. A combined opiate/oxygen/volatile anesthetic technique maybe the technique of choice for aortic aneurysm resection to ensure a hypodynamic circulation with preservation of myocardial oxygenation.

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Title: A SIMPLE TECHNIQUE FOR CONTINUOUS LUMBAR SYMPATHETIC BLOCKADE

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Introduction. Continuous lumbar sympathetic blockade can be a useful tool in the management of pain and in perioperative manipulation of lower extremity blood flow. The continuous techniques described to date utilize five to seven inch needles and a lateral approach.[1-3] We describe a simple technique using a paramedian approach at L-2 and a conventional epidural tray with a 3 1/2 inch Hustead needle.

Methods. During a two year period (7/86-7/88), unilateral continuous lumbar sympathetic catheters were placed in 33 patients after informed consent was obtained. Patient ages ranged from 18 to 42 years and weight ranged from 55 to 102 kg. Twenty-nine of the catheters were put in for perioperative sympathetic blockade for free flap (microvascular) procedures of the lower extremity. The catheters were left in place for 72 hours postoperatively, through which the patients received bolus doses or infusions of local anesthetics.

We routinely use a conventional epidural tray with a 3 1/2 inch, 18 gauge Hustead needle and a 20 gauge, closed-tip multiport catheter (Burron Perifix). The patient is placed in the prone position, with a pillow under the abdomen to straighten the lordotic curve. If the patient is unable to lie prone, then we use the lateral position (flexed at the hip) with the side to be blocked uppermost. The spinous process of L-2 is identified and the needle is inserted 3 cm lateral to the midpoint of the spinous process. The needle is directed slightly mesiad, but not cephalad or caudad. The needle is then walked along the side of the vertebral body until a "pop" or loss of resistance (LOR) is felt, indicating that the needle has exited the anterior aspect of the psoas muscle or has popped through the muscle's fibrous origin. The depth at this point will be 3-3 1/2 inches from the skin and the needle should be almost perpendicular to the coronal plane. Having done a number of these, we now have eliminated the step of walking along the vertebral body. Instead, we place the needle 3 cm lateral to the L-2 spinous process and direct it perpendicular to the coronal plane. At a depth of about 2 1/2 - 3 inches we attach an air filled syringe and use the LOR technique to identify the retroperitoneal space just anterior to the psoas. Occasionally, the hub of the needle will have to indent the skin in order to reach the correct depth. If the transverse process of L-2 is encountered, then the needle is withdrawn and a new skin wheal placed 1 cm inferior to the old one, as the needle will have to be almost perpendicular to the coronal plane to reach the necessary depth. A 3 inch needle is often too short, and may result in lumbar plexus blockade, indicative of too shallow of placement. The bevel is now aimed medial and cephalad (or caudad - it doesn't appear to matter) and 10-20 cc of local anesthetic solution injected to confirm placement (increased temperature, loss of sympathogalvanic response, no evidence of somatic blockade, etc). The catheter is then advanced 4-5 cm past the needle tip, the needle withdrawn, and catheter secured.

Results. All patients exhibited excellent unilateral sympathetic blockade of the lower extremity utilizing either an infusion or intermittent bolus technique. No problems were encountered with catheter dislodgement or migration during the operative procedure or the 72 hour post-operative period.

Discussion. We have presented a simple, effective technique for continuous lumbar sympathetic blockade using a conventional epidural tray (3 1/2 inch needle). This minimizes the need for special equipment. The paramedian approach significantly reduces the risk of renal trauma from the large gauge needle. The catheter placement lateral to L-2 obviates the need for multiple injections at several levels and also reduces the incidence of paresthesias of the lumbar plexus often seen with paramedian approaches at L-3 and L-4.

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Title: POTENTIAL ROLE FOR CIRCULATING XANTHINE OXIDASE IN MULTIPLE ORGAN DYSFUNCTION. STUDIES IN RAT LIVER

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Introduction.

Reactive oxygen metabolites play an important role in the pathogenesis of the structural and functional alterations associated with reperfusion of a wide variety of ischemic tissues. Xanthine oxidase has been postulated to be a primary source of these toxic oxygen species. It is hypothesized that during ischemia, xanthine dehydrogenase (XDH) is converted to oxygen radical-producing xanthine oxidase (XO). Upon reperfusion, XO can react with products of ATP catabolism and molecular oxygen to produce the cytotoxic oxygen metabolites, superoxide (O_2-), hydrogen peroxide (H_2O_2) and hydroxyl radical (·OH). Allopurinol, an inhibitor of XO, attenuates the tissue injury associated with ischemia-reperfusion as effectively as oxygen radical scavengers suggesting that XO is the enzymatic source of these reactive oxygen species. Evidence from this laboratory has demonstrated that paralleling the release of hepatocellular enzymes from ischemic liver is the appearance of 3-6 mU/ml of XDH + XO in the effluent. This circulating level of XO far exceeds the activity required to increase vascular permeability in nonischemic small intestine. It was the purpose of the present study to determine if infusion of XO into the vascular supply of isolated liver results in alterations in hepatocellular permeability similar to that observed with 2h ischemia/reperfusion.

Methods.

Male, Sprague-Dawley rats with body weights of 350-400g were anesthetized with an i.p. injection of sodium pentobarbital (40 mg/kg). The liver was extirpated and placed in a temperature and humidity controlled enviromental chamber. The isolated liver was then perfused with warm, oxygenated Krebs-Henselit solution via the portal vein and effluent collected from the inferior caval vein. Following an equilibration period, the liver was perfused with buffer containing 2.5, 5.0, 10.0 mU/ml or inactive xanthine oxidase. Indices of cellular injury, including AST, ALT, and LDH as well as XDH and XO activity were determined in the venous effluent during control conditions and periodically during the 2h infusion. This protocol was approved by the UAB Animal Resources Advisory Committee.

Results.

The isolated liver remained viable for at least 4h since hepatocellular enzymes and XDH/XO were not significantly altered under control (nonischemic) conditions during this period. Infusion of XO into the vascular supply of the liver at concentrations measured in the effluent of the ischemic liver (3-6 mU/ml) resulted in a dose-dependent release of hepatocellular enzymes (ALT, AST, LDH) into the effluent. Paralleling the release of hepatocellular enzymes was the appearance of XDH + XO in excess of the infused concentration.

Conclusion.

There are certainly many components to ischemia-reperfusion injury but observations in several animal models suggest that XO-derived oxygen free radicals play a major role in ischemic injury. We have previously demonstrated that 2h ischemia results in massive release of hepatocellular enzymes. Release of XDH/XO paralleled release of the hepatocellular enzymes (2). The results of the present study indicate that infusion of XO into the vascular supply of the nonischemic liver, at concentrations present in the effluent of a liver subjected to 2h ischemia/reperfusion, produces extensive tissue injury. In addition, XO is released from the liver in excess of the infused XO concentration. This evidence suggests that tremendous amounts of XO could potentially be released into the circulation from ischemic liver. The observation that XO is released from the liver in excess of the infused concentration suggests that tissue injury could potentially be amplified as the circulating XO causes release of additional XO from the liver. This circulating XO could result in formation of cytotoxic oxygen metabolites intravascularly and produce extensive damage to a variety of tissues. (Supported by DK 38681.)

XO Concentration	AST	ALT	LDH	XDH/XO
Inactive XO	23 ± 8	25 ± 7	108 ± 29	0
2.5mU/ml	25 ± 6	43 ± 9	160 ± 49	3.0 ± 0.2
5.0 mU/ml	39 ± 9	47 ± 13	215 ± 51	7.1 ± 0.4
10.0 mU/ml	31 ± 8	54 ± 8	223 ± 47	14.6 ± 1.5

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Title: SUBSTANCE P (SP) CONCENTRATION IS DECREASED IN SALIVA OF CHRONIC PAIN PATIENTS

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Introduction:

Substance P is an 11-amino acid neuropeptide that is widely distributed in the central nervous system. While it is known to be a neurotransmitter of nociceptive sensory afferents (1), it may also have analgesic action (2). Consequently, SP plasma and cerebrospinal fluid levels may be significant biological markers in chronic pain patients. The purpose of this study is two-fold. First, to determine if saliva contains significant levels of SP and second, to evaluate the relationship of SP levels in saliva and plasma in chronic pain patients and to compare these levels with healthy human volunteers (controls).

Methods:

After obtaining appropriate institutional permission, blood samples from chronic back pain patients and healthy human volunteers were collected into EDTA containing vacutainer tubes and the plasma was stored at -70 degrees centigrade until extraction. Saliva was collected from the same patients (shortly after blood samples were collected) and immediately frozen -70 degrees centigrade.

SP was extracted from plasma and saliva and measured by radioimmunoassay as described by Yanaihara et al (3). The radioimmunoassay was initiated by the addition of plasma or saliva extract to rabbit anti-SP, and radioactive SP (Iodine 125). The mixture was incubated overnight at 4 degrees centigrade. Phase separation was accomplished by the addition of an equal volume of saturated ammonium sulphate in the presence of carrier gamma globulin and centrifuged for 10 minutes. The pellets were counted for Iodine 125. Values for the SP standard curve were determined at the same time. All solutions for this assay were made in 0.05 M boric acid buffer containing bovine serum albumin, peptone and Merthiolate. SP levels were expressed per mg protein.

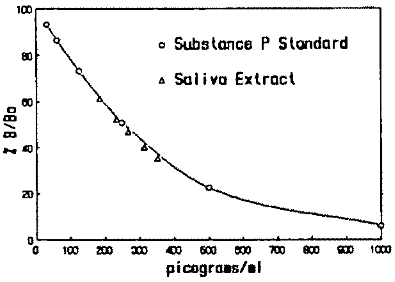

Figure 1: Correlation between saliva extract and Substance P dilution curves.

Results:

In order to demonstrate the presence of SP in the saliva, a large volume (18 ml) of saliva from healthy human volunteers was extracted and the extract was diluted serially in the same manner as the standard SP. Fig. 1 shows that the saliva extract dilution curve could not be differentiated from the standard curve prepared in buffer. This finding strongly suggests the presence of SP in saliva. Having established that SP levels can be reliably assayed in saliva, the plasma and saliva samples in both chronic pain patients and controls were analyzed for SP. The levels of SP were significantly higher in saliva than in plasma ($p < 0.01$) in both healthy volunteers and in chronic pain patients (Fig. 2). The saliva and plasma SP levels were significantly lower ($p < 0.05$) in chronic pain patients than the corresponding levels in healthy volunteers.

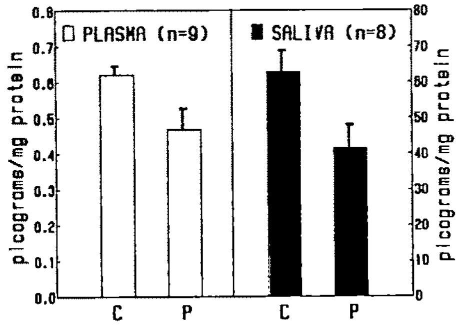

FIGURE 2: SUBSTANCE P
(C=control;P=pain patients)

Discussion:

The present observation of lower plasma levels of SP in chronic pain patients than in healthy volunteers provides fascinating clues about human perception of pain. There is an interesting reciprocal homeostatic relationship about the rates of neuronal release of SP and methionine enkephalin (MEK) in animal models. SP stimulates release of MEK in rodent cerebral slices in vitro or spinal cord in vivo (4), and SP-induced analgesia could be attributed to increased release of MEK in the nervous system. Healthy volunteers with high plasma SP levels could release greater amounts of MEK than chronic pain patients. The threshold for pain perception is, therefore, set at a lower level than in healthy volunteers. The reason for the low plasma and saliva levels of SP in chronic pain patients is not known; it may possibly be partly attributed to the differences in the rates of synthesis and metabolism of SP in chronic pain patients and healthy volunteers.

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(Supported by Medical Designs, Inc., Columbus, Ohio)

Title: EPIDURAL SUFENTANIL AS THE SOLE ANESTHETIC FOR EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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INTRODUCTION: Extracorporeal shock wave lithotripsy (E.S.W.L.) delivered with the Dornier HM-3, the most common unit in current use, produces sufficient pain to require some form of anesthesia (1). The mechanism of pain, its range of intensity, and the variables influencing that intensity are not well understood (2). While the mechanism of analgesia associated with epidurally administered opiates has been clarified, depth of analgesia, and indications for clinical use are still being investigated. This study was undertaken to determine whether epidural sufentanil provides sufficient analgesia for the performance of E.S.W.L.

METHODS: With institutional approval and informed consent, 27 patients with urolithiasis scheduled for E.S.W.L. were selected. The study population included 17 males and 10 females, with a mean age of 57 (range 29-83), mean weight of 82 kg, and mean height of 70 inches. Eighteen patients were treated for nehprolithiasis alone, including four patients who received bilateral treatment and five patients with staghorn calculi. Eight patients were treated for ureterolithiasis alone. One patient was treated for both ureteral and renal stones. Premedication was omitted. After the institution of routine monitoring, the epidural space was catheterized at the second or third lumbar interspace, guided by loss of resistance to air. Two ml of 3% 2-chloroprocaine were injected to exclude intrathecal placement. Fifty ug of sufentanil diluted with 0.9% saline to 10 ml of solution were injected as a single bolus, and E. S.W.L., usually preceeded by cystoscopy was initiated. Some subjects received 1-3 mg midazolam intravenously. A standard 1-10 pain analogue scale (3) was administered prior to placement of the epidural catheter, during cystoscopy, prior to initiating lithotripsy, and again at 1000, 2000, and 3000 shocks. At each of these points, the patient was questioned for the presence of nausea, sedation and pruritis. Outcome was considered excellent if pain scores did not exceed 1, good if pain scores did not exceed 3, fair if pain scores did not exceed 5, and poor if a single pain score exceeded 5. Complications and side effects were considered separately.

RESULTS: Excellent pain scores were obtained in 19 patients (70.3%), good in 3 patients (11.1%), fair in 2 (7.4%), and poor in 3 (11.1%). Of the patients with poor results, one had a horseshoe kidney, and one received no midazolam. No falls in blood pressure in excess of 20% of pretreatment levels were noted, and vasopressors were not administered to any patients. In one patient, despite an absence of adverse effects when 2-chloroprocaine was injected into the catheter, there was an apparent inadvertent intravascular injection associated with somnolence and apnea five minutes after the injection of sufentanil. This patient responded to positive pressure ventilation and the intravenous administration of 0.2 mg naloxone, and E.S.W.L. was completed without further difficulty. Respiratory slowing to a range of 8-12 breaths per minute was common but did not persist longer than 60 minutes after drug administration. No delayed respiratory depression was observed during prolonged postanesthetic care. Pruritis was noted in 11 patients (40.7%), but was not sufficient to require treatment. Five patients (18.5%) were nauseated in the periprocedural period, two of whom had slight or moderate emesis. The onset of mild sedation seemed common a few minutes after the administration of epidural sufentanil, but because of the concurrent administration of midazolam in some patients, no conclusions could be drawn.

DISCUSSION: While epidural analgesia using a local anesthetic is utilized commonly and successfully to facilitate E.S.W.L., this technique is not without hazards, particularly in elderly patients with limited cardiovascular reserves. The potential advantages of epidural sufentanil as the sole anesthetic or as the main component of anesthesia relate to the rapid provision of analgesia without sympathetic, motor or tactile blockade. Because sympathetic blockade has not been associated with epidural sufentanil, (4) there is no need for aggressive intravenous prehydration, and requirements for fluid resuscitation and vasopressors should be less than when epidural local anesthetics are used. Preservation of afferent sympathetic inflow may facilitate recognition of anginal pain which could theoretically be blunted in the presence of high sympathetic blockade. Patients can assist in their own positioning, and because tactile sensation is preserved, they are less likely to sustain injuries related to their positioning. Rapid onset of analgesia mitigates scheduling delays, while the presence of an epdiural catheter provides a route for the rapid institution of epidural local anesthesia if opioid analgesia should prove insufficient. The results of this study suggest that a controlled study comparing epidural sufentanil and epidural local anesthesia for E.S.W.L. would be useful.

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Title: **PROPOFOL SEDATION FOR OUT-PATIENT ENDOSCOPY - A COMPARISON WITH MIDAZOLAM.**

Authors: Patterson KW, FFARCSI, Casey PB, BSc, McEllistrem RF, FFARCSI, O'Boyle CA, PhD, Cunningham AJ, FACA.
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INTRODUCTION Propofol (2,6, diisopropylphenol) in an emulsion formulation has been extensively evaluated as an induction agent for anesthesia.The pharmacological properties of rapid distribution, short elimination half-life and early recovery suggest that propofol would be an ideal sedative agent to facilitate elective upper gastrointestinal endoscopy (1). The objectives of this study were to evaluate propofol and midazolam as sedative agents for out-patient endoscopy; to assess the anxiolytic and amnesic effects associated with both agents; and any hemodynamic and oxygen saturation changes during the procedure.

METHODS Following institutional ethics committee approval and informed consent, 40 patients (ASA I-II) scheduled for elective upper gastrointestinal endoscopy were randomly allocated to two groups. Group 1 (n=19) received midazolam 81 ±32 µg/kg. Group 2 (n=21) received propofol 0.95 ± 0.4 mg/kg. Both drugs were titrated to clinical end-points of sedation - slurred speech, ptosis and nystagmus. Monitoring included oxygen saturation (Critikon Oxy-shuttle), automatic blood pressure (Dinamap) and EKG (Hewlett Packard). Anxiety levels, using a visual analogue scale (VAS) were assessed pre-operatively and 30 minutes post-injection. Psychomotor function, using the digit symbol substitution test (DSST), was assessed pre-operatively, at 30 and 90 minutes following drug administration (2,3) by a blinded observer. The degree of amnesia was assesed with a modified visual memory test of McKay and Dundee and a subjective questionnaire (4). Endoscopy was performed using an Olympus Q10 endoscope by the same endoscopist who rated patient co-operation and operating conditions on a visual analogue scale. Data are presented as mean ± SEM. Statistical analysis included the Chi-Squared, Mann-Whitney U and Wilcoxon Matched Pairs tests. A p value less than 0.05 was considered significant.

RESULTS The changes in DSST scores from pre-op to 30 and 90 minutes post-injection for both groups are illustrated in Figure I. A significant deterioration from pre-op to 30 minutes post-injection was noted in group 1 ($p<0.002$). The changes in VAS score are illustrated in Figure II. All patients were amnesic up to endoscope removal. A significant number of patients in group 2 remembered endoscope removal ($p<0.001$). Oxygen desaturation ($S_aO_2 \leq 90\%$) was observed in 5 out of 19 patients in the midazolam group and 4 out of 21 patients in the propofol. A significant increase in heart rate and reduction in mean arterial pressure was noted in both groups. Operating conditions and patient cooperation were similar in both treatment groups.

FIGURE I: PSYCHOMOTOR FUNCTION

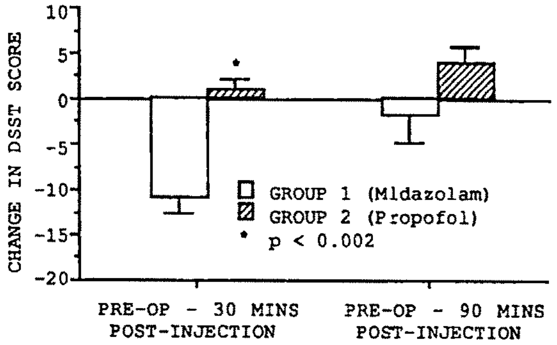
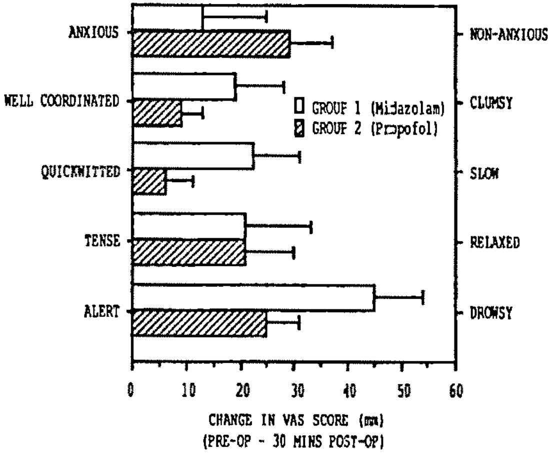


FIGURE II: VISUAL ANALOGUE SCALE (VAS)



DISCUSSION Propofol in doses of 0.95 ± 0.4 mg/kg has similar amnesic and anxiolytic properties when compared with midazolam (81 ± 32 µg/kg). Propofol with its rapid and extensive distribution and short elimination half-life ensured an early return to street fitness in this patient population. Hypoxemia and cardiovascular depression can occur with the administration of sedative doses of propofol and midazolam to facilitate outpatient endoscopy. EKG, blood pressure and oxygen saturation monitoring for these cases should be employed, especially if patient access is limited and if the procedure is performed in darkened surroundings.

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Title: THE POTENCY OF SUCCINYLCHOLINE ON THE MASSETER AND ADDUCTOR POLLICIS MUSCLES IN CHILDREN

Authors: MH Plumley, M.B., JC Bevan, M.D., JM Saddler, M.B., F Donati, M.D.*, DR Bevan, M.B.*

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Introduction. The masseter is one of the important muscles that influences jaw opening[1] and maintains airway patency. Adequate jaw relaxation is required for ideal intubation conditions. Succinylcholine is associated with decreased mouth opening in a large number of patients[1] and with masseter muscle rigidity (MMR), a condition that has an incidence of approximately 1%[2]. This phenomenon occurs when the peripheral muscles are blocked but it is unknown whether neuromuscular transmission at the masseter is blocked to the same degree. This study was therefore designed to determine the sensitivity of the masseter to succinylcholine in children anesthetized with halothane and nitrous oxide.

Method. Twenty children aged 3-10 years taking no medications were studied following institutional approval and informed parental consent. The patients were ASA I, unpremedicated and scheduled for elective day care surgery requiring general anesthesia with endotracheal intubation for dental or E.N.T. procedures. Patients with neuromuscular disease or abnormalities of jaw opening were excluded. Anesthesia was induced with halothane, N_2O (66%) and O_2 (34%) and atropine 0.01 mg.kg^{-1} intravenously. Endotracheal intubation was performed under deep halothane anesthesia. Skin electrodes were placed below each zygomatic arch, anterior to the mandibular condyles in close proximity to the nerve supplying the masseter. A force transducer system was attached to a securely taped oral airway and to a metal frame fixed to the operating table[3]. Supramaximal train of four stimuli were applied every 12 seconds to the ulnar nerve and the nerve to masseter and the evoked twitch response was recorded. Succinylcholine 0.15, 0.25, 0.5 or 1.0 mg.kg^{-1} was given by random allocation and recording continued until there was full recovery for both muscles. Dose response curves were constructed by linear regression analysis of the probit value of the percentage reduction of first twitch height plotted against log dose to obtain ED50, 90, 95 values ± SEM and were compared by paired "t" test. Onset times to maximum block were expressed as mean ± SEM.

Results. The succinylcholine groups did not differ significantly for age, weight or height. The masseter was significantly more sensitive to succinylcholine than the adductor pollicis (Table I and Figure 1). The overall mean onset time of maximum twitch depression was shorter for the masseter 40.0 ± 3.7 s than for the adductor pollicis 60.0 ± 6.0 s ($p<0.01$). There was no significant difference between the duration of maximum twitch depression for the two muscles.

Discussion. This study showed that, in children, the masseter muscle is more sensitive than the adductor pollicis to succinylcholine therefore reported increases in masseter resting tone are not due to inadequate block of neuromuscular transmission. The normal intubating dose of succinylcholine (1.0 - 2.0 mg.kg^{-1}) is 4-6 times the ED90 value determined in this study for the masseter. The ED90 for the adductor pollicis (0.37 mg.kg^{-1}) appears larger than the ED90 determined for adults[4] (0.29 mg.kg^{-1}) despite the use of halothane in this study.

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FIGURE 1

Potency of succinylcholine at the masseter and adductor pollicis muscles in mg.kg^{-1} (bars = SEM)

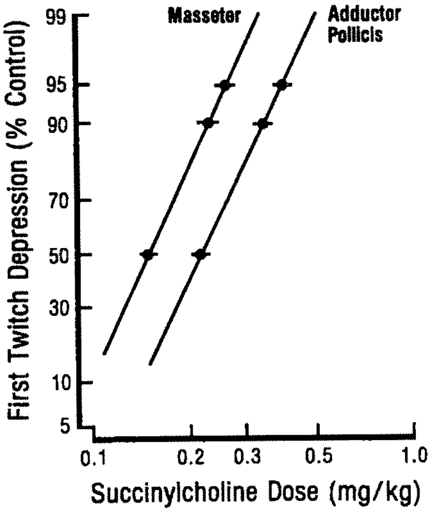

TABLE 1

	Adductor Pollicis	Masseter
ED50	0.24 ± 0.03	0.17 ± 0.01 *
ED90	0.37 ± 0.04	0.25 ± 0.01 *
ED95	0.44 ± 0.05	0.28 ± 0.02 *

* $p < 0.02$

Mean values in mg.kg^{-1} ± SEM

Title: SUCCINYLCHOLINE AND INCREASED RESTING JAW TENSION IN CHILDREN

Authors: MH Plumley, M.B., JC Bevan, M.D., JM Saddler, M.B., F Donati, M.D.[*], DR Bevan, M.B.[*]

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Introduction. Masseter muscle rigidity (MMR) has a reported incidence of approximately 1% in children given halothane and succinylcholine[1]. A recent study[2] has reported an increase in mean jaw stiffness following succinylcholine in children, suggesting that MMR may be an exaggerated form of this response. This study was designed to determine (i) whether these changes in jaw tone were dose related, (ii) whether similar changes could be observed in the adductor pollicis muscle and (iii) to investigate the temporal relationship between the neuromuscular blockade and changes in masseter resting tone.

Methods. Twenty ASA I, unpremedicated children aged 3-10 years taking no medications were studied following institutional approval and informed parental consent. Patients with neuromuscular disease or abnormalities of jaw opening were excluded. Anesthesia was induced with halothane, N_2O (66%) and O_2 (34%) and atropine 0.01 mg.kg^{-1} administered intravenously. Endotracheal intubation was performed under deep halothane anesthesia. Skin electrodes were placed below each zygomatic arch, anterior to the mandibular condyles close to the nerve supplying the masseter. A force transducer system was attached to a securely taped oral airway and to a metal frame fixed to the operating table[3]. Supramaximal train of four stimuli were applied every 12 seconds to the ulnar nerve to masseter and the evoked twitch response was recorded. Succinylcholine, 0.15, 0.25, 0.5 or 1.0 mg.kg^{-1}, was given by random allocation. Linear regression analysis of the change in baseline tension against dose was performed. Time to onset, maximum effect and duration were measured for resting tension increases for both muscles and were compared by paired student's "t" test.

Results. The groups did not differ significantly for age, weight or height. Both muscles consistently showed increases in resting tension which was significantly dose related ($p < 0.0034$ for the masseter and $p < 0.012$ for the adductor pollicis. Table I). However, mean tension increases were higher for the masseter than for the adductor pollicis. Onset of resting tension increases were shorter for the masseter (12.6 seconds ± 1.3 SEM) than for adductor pollicis (17.7 seconds ± 1.36 SEM) ($p < 0.02$). Maximum resting tension was reached after 31.0 ± 2.8 s and 24.0 ± 2.4 s for the adductor pollicis and masseter respectively ($p < 0.02$). The duration of this phenomenon was not significantly different (62.6 ± 7.7 s for adductor pollicis v. 74.1 ± 21.4 s for the masseter) and was observed after maximum twitch depression for any given dose and during the recovery of neuromuscular transmission at both the adductor pollicis and masseter muscles. Maximum twitch depression occurred at 60.0 ± 6.0 s and 40.0 ± 3.7 s for the adductor pollicis and masseter respectively ($p < 0.01$). Overall duration of twitch depression was 230.0 ± 22 s and 217.0 ± 22 s for the adductor pollicis and masseter respectively.

Discussion. This study demonstrated that succinylcholine causes dose related increases in masseter tone. This phenomenon occurred for the adductor pollicis to a much lesser degree. This was seen during maximum twitch depression and could be due to a direct action of succinylcholine on the muscle. Increased tension might be a normal response to succinylcholine which is not limited to the masseter and MMR may be an exaggerated form of this response. The faster onset for the masseter may be due to a faster circulation time following a bolus injection.

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3. Smith CE, Donati F, Bevan DR. Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. Can J Anaesth 1988; 35:S124.

TABLE I

Succinylcholine Dose In mg.kg^{-1}	Adductor Pollicis	Masseter
0.15	1.0 ± 1.1	8.4 ± 2.5
0.25	4.7 ± 1.0	27.5 ± 4.4
0.50	6.2 ± 0.9	40.5 ± 17.8
1.00	9.1 ± 2.3	51.6 ± 16.8

Maximum tension generated in the adductor pollicis and masseter muscles. Mean values in grams ± SEM

TITLE: **ADEQUATE SERUM LIDOCAINE LEVELS FAIL TO CONTROL THE HEMODYNAMIC RESPONSE TO INTUBATION**

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Introduction. Lidocaine has been used to blunt the cardiovascular responses to endotracheal intubation. Various modes have been employed: intravenous (1-3), nebulized (4) and intratracheal (2). Studies have focused on hemodynamic responses; however few investigators have measured serum lidocaine levels at the time of intubation. It is possible that differences in cardiovascular responses may in part be due to differences in blood lidocaine levels following doses given intravenously vs. intratracheally.

The purpose of this study is to determine serum lidocaine levels at the time of intubation following aerosolized and/or intravenous administration and to correlate them with the hemodynamic response to intubation.

Methods. Following approval by our investigational review board and receipt of informed consent from our patients, forty ASA I and II patients were randomly assigned to one of four treatment groups. Within a span of 15 min, as detailed below, each patient received either lidocaine or placebo by nebulizer, followed by lidocaine or placebo by IV push. Both patient and anesthesiologist were blinded as to the contents of nebulizer and syringe.

Procedures for study drug administration and for anesthetic induction were precisely defined and followed. Nebulized lidocaine (4 mg/kg) or an equivalent volume of saline were given over a 10 min period in the holding area. The patient immediately entered the OR, where automated recordings (Datascope) of heart rate and systolic, diastolic and mean blood pressure were initiated (= 0 min) and repeated at 1 min intervals thereafter. At 2 min, dTC (3 mg) was given and followed with O_2 by mask. At 4 min, either lidocaine (2 mg/kg) or saline was given intravenously, followed immediately by thiopental (5 mg/kg) and then succinylcholine (1.5 mg/kg). Laryngoscopy was begun at 5 min and maintained for exactly 45 sec before passage of the ET tube and mechanical ventilation with either 1.5% isoflurane or 2% enflurane in $O_2/N_2O = 2/4$ L/min. At the time of intubation (2 minutes after IV lidocaine or placebo was given) venous blood was obtained from the antecubital fossa in the arm opposite the intravenous site. The patient was left undisturbed for an additional 6 min of hemodynamic recordings, at which point the study was terminated. The serum was stored at -20 C until assay by the EMIT method. This method was unable to detect serum lidocaine levels at less than 0.5 mg/L.

Results. Thirty-eight samples were obtained from 40 patients. In the ten patients who received both nebulized and IV saline and in the nine patients who received nebulized lidocaine and IV saline, serum lidocaine levels were undetectable at the time of intubation. In ten patients who received nebulized saline and IV lidocaine, serum lidocaine levels range from 1.8 to 14.6 mg/L (x=5.2 mg/L). In nine patients who received nebulized saline and IV lidocaine, serum lidocaine levels ranged from 1.0 to 5.0 mg/L (x=3.2 mg/L). There was no significant difference in serum lidocaine levels between the IV lidocaine group and the IV plus aerosolized lidocaine group ($P>0.05$ by Mann-Whitney U-test).

There were no differences among the groups for any of the hemodynamic variables measured prior to intubation ($P<.05$ by ANOVA). HR, SBP, DBP AND MBP all showed significant increases during intubation within each of the four patient groups ($P>.05$ by paired t-test). However, those post-intubation maximum values did not differ significantly among the four treatment groups, despite different blood lidocaine levels.

Discussion. Minimal blood lidocaine levels effective in supression of premature ventricular contraction ranges from 0.6-2 mg/L while objective signs of lidocaine toxicity are thought to be 5-6 mg/L (5). Our study demonstrates that lidocaine levels which averaged in high normal range had no effect on the hemodynamic response to intubation. Our findings are similar to Chraemmer-Jorgenson, et al (1) who in a double blind study in healthy women showed no effect on the hemodynamic response of 1.5 mg/kg IV lidocaine vs placebo given 2 minutes before intubation. In contrast Abou-Madi, et al (3) reported a borderline blunting of heart rate and blood pressure in patients who received 1.5 mg/kg IV lidocaine 2-3 minutes before intubation. Their lidocaine levels 2-3 minutes after administration averaged 1.86 mg/L.

We found undetectable (<0.5 mg/L) serum lidocaine levels after nebulization. Macon, et al (6) also found low lidocaine levels (less than 1.0 mg/L) 15 minutes after administration of 600 mg of the aerosolized drug. Our patients received a lidocaine dose of 4 mg/kg (never > 400 mg) by nebulizer. Chimm, et al (7) also found low serum levels of lidocaine (0.4 mg/L) 10 minutes after administration of 400 mg of the nebulized drug.

Our study demonstrates that the hemodynamic responses to endotracheal intubation are not blunted by high serum lidcoaine levels. Furthermore, blood levels following intratracheal administration of up to 400 mg of nebulized lidocaine is negligible.

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Title: EPIDURAL SUFENTANIL ALONE FOR ANALGESIA FOR LABOR AND DELIVERY

Authors: GM Powell, M.D. and RB Steinberg, M.D.
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Introduction. Continuous lumbar epidural analgesia using local anesthetics is a standard method of providing control of pain during labor and delivery. Recent work has shown that epidural and intrathecal opiates can be used to provide pain relief during the first stage of labor thus avoiding the sympathetic blocking effects of local anesthetics (1). The analgesia using epidural opiates has been only moderate when they are used alone (2,3). Consequently they have instead been used in combination with reduced dosages of local anesthetics in order to try to achieve improved analgesia with a lower incidence of side effects. We reasoned that sufentanil, being highly lipid soluble and very potent as a mu-receptor agonist, might prove effective alone as an analgesic for the first stage of labor.

Methods. After approval by the Medical Research Committee, sixty healthy adult (18 y.o.) parturients who requested epidural analgesia agreed to participate in the study. The patients were divided into six groups of ten receiving, respectively, 5, 10, 20, 30, 40, and 50 mcg. of sufentanil epidurally. Subsequent epidural doses were given when requested by the patient, in accordance with our usual practice. Neonates were evaluated by calculating Apgar scores and, labor pain was measured with a Visual Analog Scale. Patients were asked to assess the most painful part of a contraction prior to the epidural test dose; 10, 20, and 30 minutes after the dose of sufentanil; and at the time that the patient requested a subsequent dose. The duration of analgesia was defined as the time from the sufentanil dose to the patient's request for additional analgesia. Data were analyzed by one way analysis of variance and Student's t-tests.

Results. Fifty-six parturients completed the study. Two patients were excluded because they delivered precipitously and two were excluded because of poor catheter placement. The patients in the six groups were comparable in terms of age, height, weight, parity (approximately 1:1 primip:multip), and baseline VAS. Ten minutes after the administration of sufentanil, there was a highly significant reduction in VAS scores in all groups (Figure). Patients given 50 mcg of sufentanil had significantly lower pain scores at 10 and 20 min than did patients given 5 mcg or 10 mcg (Figure). Seven parturients obtained satisfactory pain relief for the remainder of their labor, and delivered vaginally without additional epidural analgesia. Data from these patients excluded from analysis of the duration of analgesia. The duration of analgesia increased with increasing doses of sufentanil ranging from 79 min to 138 min with 5 mcg and 50 mcg respectively. The overall relationship was significant (p=0.048). The parturients experienced few side effects (pruritis, dizziness, mild sedation), most of which required no treatment. There were no neonatal complications. All Apgar scores exceeded 7 at 5 and 10 min.

Discussion. Epidurally administered sufentanil provided highly effective analgesia during the first stage of labor without affecting motor function and with minimal effects on hemodynamics. The principle dose effect appeared to be an increase in duration at higher dosages, a result in agreement with the findings of Hughes when using sufentanil for post-cesarean pain (4). Duration was short, approximately two hours, and it remains to be seen if accumulation prohibits repeated dosing or infusion. Seven patients experienced vaginal delivery without need for additional analgesia. This result contradicts earlier studies in which epidural narcotics did not provide satisfactory pain relief for the second stage of labor (2,3) and suggests that sufentanil is a more potent epidural analgesic than the other narcotics studied. Although standard neonatal evaluation revealed no adverse effects, detailed neonatal neurobehavioral testing might have revealed subtle effects which were not appreciated during routine observation.

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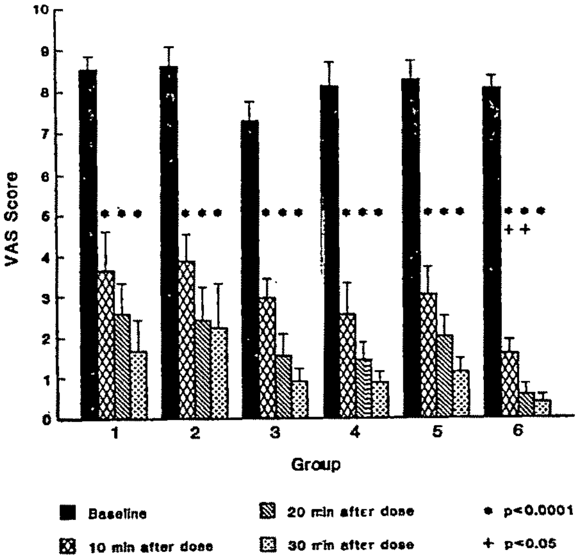

Title: THE FATE OF AIR EMBOLI IN THE PULMONARY CIRCULATION OF THE DOG

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Introduction. The lung acts as a filter for air entering the venous circulation[1]. In a preliminary report, obstruction of pulmonary arterioles by air emboli has been reported[2]. However, the mechanism by which the lung filters and excretes gas emboli remains unknown. Our objective was to determine the location in the pulmonary circulation from which air emboli are eliminated, and the mechanism by which they are eliminated.

Methods. Following the approval of the Animal Care Committee, six adult dogs were anesthetized with pentobarbital (30 mg/kg), intubated and mechanically ventilated. Catheters were placed in the femoral arteries and veins, and in the pulmonary artery. Following catheter placement, a thoracotomy was performed in the ninth left intercostal space and a transparent window was implanted[3]. With the dog on its right side, 5 ml of a suspension of microbubbles (60 um diameter) produced by agitation of air with plasma, was injected into a Swan Ganz catheter with its tip fluoroscopically placed in the segmental artery supplying the vessels under the window. The elimination of the bubbles from the pulmonary circulation was observed through the thoracic window with a Leitz Ultropak microscope coupled to a COHU 4400 television camera, and recorded with a Panasonic AG 7300 SVHS recorder. After returning to baseline, a second 5 ml bolus was injected, immediately followed by interruption of blood flow in the field by inflation of the Swan Ganz balloon and application of 10 cm H_2O of PEEP. Bubble radii were measured from the videotapes and their rate of elimination was then calculated by plotting bubble radius versus time. The rates under control conditions were compared to the rates under ischemic conditions for each animal using a Student's t-test for paired samples. All other measured physiologic variables, including pulmonary artery pressure, cardiac output, and results of arterial blood gases were also compared using a Student's t-test for paired samples.

Results. All air emboli lodged in the pulmonary arterioles where they either steadily decreased in size until they were entirely eliminated, or upon reaching a critically small size (radius $\sim$5 um) entered the capillary bed. The elimination rates expressed in terms of change in bubble radius over time are shown in table 1. The elimination rates under control and zone 1 conditions were not significantly different ($P > .80$). There were no significant differences in other physiologic variables between the two groups.

Discussion. These results indicate that venous air emboli are eliminated primarily in pulmonary arterioles. Their elimination is not dependent on regional perfusion, but appears to result primarily from molecular diffusion of gas across the arteriolar wall into alveolar spaces. These findings confirm predictions made by Chang[4] using a model of branching capillary tubes that bubbles would lodge in arterioles because of surface tension. However, the unimportance of regional perfusion in the elimination of pulmonary air emboli is a departure from routine concepts of gas exchange in the lung. Further studies using gases with different solubilities and diffusivities may yield different results.

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Table 1: Average rate of bubble radius decrease in um/min. (± SEM)

dog	control	zone 1
1	7.26 ± 0.99	7.99 ± 0.71
2	4.73 ± 0.35	4.36 ± 0.45
3	8.17 ± 0.86	7.17 ± 0.58
4	4.85 ± 0.84	5.35 ± 1.00
5	5.33 ± 1.90	7.19 ± 0.98
6	9.61 ± 1.20	8.64 ± 0.69
mean	6.66 ± 2.00	6.78 ± 1.60

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Title: AN EVALUATION OF INTERPLEURAL ANALGESIA WITH ETIDOCAINE IN CHILDREN

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Introduction. Interpleural instillation of local anesthetics to provide postoperative analgesia was first described in 1986 (1). Since that time, this technique has been used in both children and adults in a variety of clinical settings (1, 2, 5). The ideal local anesthetic agent for this purpose and its optimal dosage has yet to be determined (6). This study evaluated the safety and efficacy of interpleural etidocaine.

Methods. The patient population consisted of four children, ages 2 to 18 years. Three patients underwent repair of pectus excavatum. The fourth patient studied was a victim of multiple trauma. With approval of the Human Investigation Committee and written informed parental consent, blood samples were obtained and plasma concentrations determined following interpleural instillation of etidocaine. Interpleural catheters (three of which were bilateral) were placed at operation under direct vision. After a test dose of 3 ml of normal saline with 5 ug/ml epinephrine in each catheter, a total dose of .3 ml/kg of 1% etidocaine with 5 ug/ml epinephrine was injected over two minutes. Blood samples were obtained at 2, 5, 15, 30, 60, and 120 minutes after injection. Plasma etidocaine levels were measured using gas chromatography, and the duration of analgesia achieved was determined by the need for supplemental opiates.

Results. Mean plasma etidocaine levels are indicated in Table 1. In the children, post pectus repair maximum plasma etidocaine concentration was reached in 5 to 30 minutes and ranged from 1.40 to 2.13 ug/ml, with a mean value of 1.77 ± 0.37. In the fourth patient, age 18 years, who had a severe liver laceration and pulmonary contusion, the maximum etidocaine level was 3.75 ug/ml (Table 2). The duration of analgesia was 5 to 12 hours with a mean value of 8.3 hours.

Discussion. Etidocaine was evaluated for interpleural analgesia in a group of pediatric patients. Etidocaine and bupivacaine have previously been used in intercostal nerve blocks (4), while only bupivacaine has been reported for use in the interpleural space (1, 2, 5). The simplicity of interpleural catheter placement makes it an attractive alternative to multiple intercostal nerve blocks.

Because of its long analgesic effect and widespread use in anesthesia, bupivacaine has been the drug used most frequently for interpleural analgesia. Etidocaine also is noted to have prolonged analgesic effects and offers some pharmacokinetic advantages over bupivacaine. These include a much larger volume of distribution, a more rapid plasma clearance, and a greater uptake into lung tissue. This should reduce the risk of systemic toxicity. In this study peak plasma etidocaine levels did not approach the toxic range in the patients with normal liver function.

McIlvaine et al (3) reported his experience with continuous interpleural infusion of .25% bupivacaine and demonstrated significant drug accumulation at 24 hours. In the one patient in this study with high plasma levels of etidocaine, there was a concomitant major hepatic injury. This patient had also been previously injected with .25% bupivacaine through an indwelling pleural catheter. Plasma levels of both etidocaine and bupivacaine remained elevated for 6 and 14 hours after injection respectively (Table 2).

This study demonstrates that etidocaine can be safely used to produce interpleural analgesia in children without hepatic injury. The duration of action is similar to that achieved with bupivacaine, and the more rapid plasma clearance of etidocaine reduces the risk of systemic toxicity. This effect should be magnified when a continuous interpleural infusion is used. The favorable pharmacokinetic properties of etidocaine may make it the drug of choice for interpleural use. Further studies are now in progress.

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Table 1. Plasma Levels of Etidocaine Following Interpleural Injection

Time (Mins)	2	5	15	30	60	120
Mean ISD (ug/ml)	1.21 ±0.18	1.54±0.20	1.56±0.56	1.31±0.78	0.81±0.46	0.5±0.12

Table 2. Plasma Levels of Etidocaine and Bupivacaine in Patient #4

Time (Min)	0	2	5	15	30	60	120	360
Etidocaine	0.08	1.52	2.21	3.75	3.69	3.28	2.51	.77
Bupivacaine	2.14	2.21	1.63	1.54	1.23	1.22	1.07	.48

(Time 0 = The time of etidocaine injection, 8 hours after bupivacaine injection)

TITLE: PLASMA CHOLINESTERASE LEVELS IN CANCER PATIENTS TREATED WITH CHEMOTHERAPY

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Introduction: Cancer patients may have low plasma cholinesterase (PCh) levels either due to their disease process or because of treatment with chemotherapy drugs.[1] As such, they may be at risk for prolonged neuromuscular blockade after succinylcholine administration. To date, Cytoxan is the only chemotherapy agent shown to induce low PCh levels[2]. The following study was undertaken to assess the relative influence of other chemotherapeutic agents on PCh levels in cancer patients.

Methods: The preoperative blood samples of 70 cancer patients scheduled for elective surgery were analyzed for PCh levels using the photometric method of Ellman et al.[3] Whenever a low PCh value was detected (<1900 mU/ml), the presence of atypical cholinesterase was ruled out by determining the dibucaine number (D.N.) using the method of Kalow et al.[4] Those with abnormal D.N. were excluded from further consideration.

The remaining patients were divided into two groups: Group 1 consisted of patients who had received chemotherapeutic agents; Group 2 consisted of those not treated with chemotherapy. The medical records of the Group 1 patients were reviewed in detail to determine which chemotherapeutic agents they had received. In addition, their liver function tests were recorded to rule out a hepatic cause for low PCh values.

Between-groups comparisons for PCh values were performed using Student's t-test for non-paired data. P<.05 was regarded as significant.

Results: Of the 70 patients in this study, we found 7 who were excluded due to dibucaine numbers indicative of genetically - determined atypical cholinesterase (D.N.<70%). No patient was excluded because of abnormal liver function tests.

Among the remaining patients, PCh values in group 1 (n=32) were significantly lower than those in group 2 (n=31): Mean values = 2151 mU/ml ± 106 SE versus 2654 mU/ml ± 92 SE, respectively, P<.05.

The chemotherapeutic agents given to the Group 1 patients are summarized in Table 1. Since some patients received multiple agents, the total of the numbers shown is greater than the sum total of the patients studied. As expected, a high incidence of low PCh levels was observed in those who received Cytoxan, either alone or in combination with other drugs. Among the remaining agents, those with the highest incidence of low PCh levels are shown in capitals. These were: Adriamycin, Cytosine Arabinoside, Cisplatin, Carboplatin, Fluorouracil, Floxuridine, Idarubicin, Methotrexate, and Vinblastine.

TABLE 1

CHEMOTHERAPEUTIC AGENT	# PTS.	# WITH LOW PCh LEVELS	# WITH CYTOXAN IN COMBINATION
Alkeran	1	0	0
ADRIAMYCIN	9	4	2
CYTOSINE ARABINOSIDE	3	2	0
Actinomycin-D	1	0	0
Carmustine	2	0	0
Bleomycin	3	0	0
CISPLATIN	11	3	2
Cytoxan	7	5	5
CARBOPLATIN	1	1	0
Lomustine	1	0	0
FLOXURIDINE	1	1	0
FLUOROURACIL	3	1	0
IDARUBICIN	1	1	0
Mitomycin-C	2	0	0
METHOTREXATE	7	2	1
Etoposide	4	0	0
VINBLASTINE	7	2	1

Discussion/Conclusions: The PCh values of cancer patients receiving chemotherapy may be significantly lower than those of patients who have not received chemotherapy. We found many agents in addition to cytoxan to be responsible for low PCh levels.

We conclude that PCh levels in cancer patients treated with chemotherapy agents are often low enough to result in prolonged neuromuscular blockade following succinylcholine administration. The low PCh levels appear to be independent of drug or disease-induced hepatic dysfunction. Our data suggest that the potential advantages of succinylcholine should be weighed carefully relative to its very predictable risks in this patient population.

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TITLE: EFFICACY OF A NEW LOCAL ANESTHETIC - 0.5% ROPIVACAINE - FOR BRACHIAL PLEXUS BLOCK

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Introduction. LEA 103, Ropivacaine is a new local anesthetic whose chemical formula is similar to that of other amino amides in clinical use. In animal and volunteer studies, Ropivacaine has been shown to be a potent long acting local anesthetic with an effective duration similar to bupivacaine(1) but with lower arrhythmogenic potential(2). The main objective of the present study was to assess the efficacy and safety of 0.5% Ropivacaine in brachial plexus blockade.

Methods. After gaining approval from the Institutional Review Board and obtaining informed written consent sixteen ASA Class I or II adult patients (ages 23-56, weight 60-100kg), who were scheduled for elective surgery of the upper extremity were enrolled in this open label study. There were two groups of eight patients each, Group I received 0.5% Ropivacaine without epinephrine and Group II received the drug with epinephrine in a concentration of 1:200,000. Prior to the administration of the premedication of 0.15 mg/kg morphine sulfate IM each patient had a baseline sensory and motor exam of the extremity to be blocked.

The drug was administered via the subclavian perivascular approach with 3 ml test dose followed by 30 ml as the main dose. The intercostobrachial nerve was blocked in the axilla with 5 ml of the drug. Efficacy observations were made based on sensory analgesia and motor blockade.

The sensory blockade was assessed and graded as 0 being no loss of sensation to pinprick, 1 being analgesia (feels touch but not sharp) and 2 being anesthesia (does not feel touch). Motor blockade was assessed at the shoulder and hand with 0 being no weakness, 1 being paresis and 2 being paralysis. Testing was done in the C2 through T2 dermatome distributions at 2, 5, 10, 15, 20, 25, and 30 minutes. After 30 minutes, checks were performed every 15 minutes until 5 hours after the injection and then every 30 minutes until 12 hours after the injection and then every hour until complete resolution of the block.

Safety observations were made on the basis of any change in blood pressure, heart rate or evidence of CNS toxicity.

Data was analyzed utilizing analysis of variance for repeated measure with T test using the analysis of variance error terms. A p value of <0.05 was considered significant.

Results. The incidence of successful anesthesia was 100% in the C6 through T1 dermatomes with no patients requiring supplemental blocks. (Fig 1.) Motor block was also profound with all patients developing paralysis at both the shoulder and hand. Both groups had rapid onset of analgesia and anesthesia with prolonged duration. Although onset and duration times appear shorter in Group II, this difference was not statistically significant. (Table I) At each time period the number of dermatomes developing anesthesia was greater in Group II, although this difference was statistically significant only at 25 and 30 minutes. (Table II)

The dose of the drug which was administered in this study ranged from 1.90 mg/kg to 3.28 mg/kg. With this dose no patient developed any adverse reactions suggesting signs of cardiovascular or CNS toxicity. All patients had full return of sensory and motor function.

Discussion. Ropivacaine both with and without epinephrine seems to provide a rapidly progressive block of prolonged duration with excellent analgesia and motor paralysis. Ropivacaine consistently produced adequate surgical anesthesia such that no supplementation was needed. The motor block provided by this drug appears to be more profound than what is usually seen with either 0.5% bupivacaine or 1% mepivacaine. Whereas the duration of analgesia is comparable to that of 0.5% bupivacaine when used for brachial plexus block, it appears to have a more rapid onset. Undoubtedly, further comparative studies need to be done in order to confirm these observations. Overall, 0.5% Ropivacaine appears to be a safe and effective new local anesthetic which is clinically useful for brachial plexus blockade.

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Figure 1

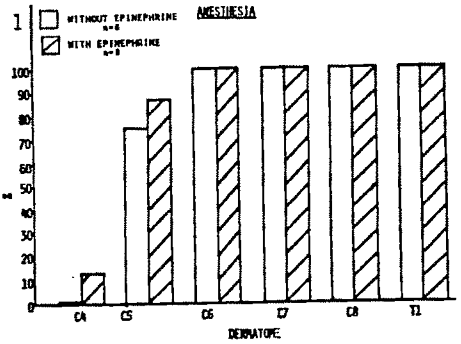

Table I

	Onset in Minutes		Duration in Minutes	
	Grp. I	Grp. II	Grp. I	Grp. II
Analgesia	5.00 ± 6.21	4.00 ±3.70	821.50 ±114.75	754.50 ±156.90
Anesthesia	17.13 ±24.00	8.00 ±6.50	671.88 ±151.84	622.00 ±128.78

Table II ANESTHESIA (C_4-T_1)--NUMBER OF DERMATOMES ± S.D.

Time in Minutes	2	5	10	15	20	25	30
Ropivacaine 0.5% Group I	.5 ±1.41	.88 ±1.73	1.5 ±1.60	2.0 ±1.85	2.38 ±1.77	2.75* ±1.83	3.00# ±1.93
Ropivacaine 0.5% with Epinephrine Group II	.63 ±1.06	1.25 ±1.04	2.13 ±1.55	2.75 ±1.45	3.13 ±1.46	3.63* ±1.61	4.13# ±1.36

* P <.05, # P <.02

Study supported by a grant from Astra Alab AB and performed at Medical Center and Audie Murphy VA Hospitals in San Antonio, Texas

Title: ATTENUATION OF CARDIOVASCULAR EFFECTS OF KETAMINE ANESTHESIA BY MIDAZOLAM: A DOSE-RESPONSE STUDY

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Introduction. Midazolam, a water soluble, short acting benzodiazepine, has been shown to be effective in attenuating the increases in blood pressure and heart rate produced by intravenous administration of ketamine (1,2,3). The current investigation was undertaken to study the effect of varying the dose of midazolam on the cardiostimulatory actions of ketamine anesthesia.

Patients & Methods. The study was approved by the ethical committee of the hospital and informed consent was obtained from the patients. One hundred and twenty unpremedicated healthy women (ASA physical status I or II, ages 25-58 yrs) undergoing minor gynaecologic surgery under general anesthesia were included in the study. Patients with hypertensive, coronary artery or cerebrovascular disease, those on concurrent drug therapy or with a history of psychiatric disorders were excluded. The patients were randomly allocated to one of four groups. Group 1 received 50 mcg/kg, group II 75 mcg/kg, group III 100 mcg/kg and group IV 125 mcg/kg of midazolam intravenously via an indwelling cannula placed in a superficial vein on the dorsum of the hand. Three minutes after the administration of midazolam general anesthesia was induced with intravenous ketamine (2 mg/kg) and maintained with 66% nitrous oxide in oxygen administered using a semi-closed, non-rebreathing Mapleson A circuit. Spontaneous respiration was maintained throughout and increments of ketamine (10 mg) were given intravenously during the procedure as judged necessary by the anesthesiologist. Systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures were measured every minute using a non-invasive, automatic blood pressure measuring device (Dinamap, Critikon, USA). Electrocardiogram was monitored routinely throughout the study period. Baseline blood pressures and heart rate (HR) were measured prior to the administration of midazolam. Parametric data were analysed for statistical significance using anova and results considered significant at $p < 0.05$.

Results. The four groups in the study were comparable in terms of age and weight. There was no statistically significant difference between the groups in the induction dose, total dose of ketamine received and the duration of anesthesia. Significant increases in MBP and DBP were observed in all the four groups during post-induction and intra-operative periods (Table). Similar increases in SBP were observed in groups I and IV. Except in group III during intraoperative period heart rate increased significantly in all the four groups.

Discussion. This study fails to support the notion that midazolam pretreatment reliably attenuates the increases in blood pressure and heart-rate produced by ketamine anesthesia. Failure of our study to confirm the recent reports of beneficial hemodynamic effects of midazolam-ketamine combination (1,2,3) may be due to the differences in the dose of ketamine used and the time at which midazolam was administered prior to ketamine anesthesia.

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Table: HAEMODYNAMIC CHANGES (Mean ± S.D.)

	BASELINE	POST-INDUCTION	INTRA-OPERATIVE
GROUP I (n=30)			
SBP	121.4 (11.0)	134.6 (12.9)*	134.4 (13.9)*
DBP	75.0 (10.7)	89.3 (9.3)*	85.6 (9.8)*
MBP	90.4 (9.8)	103.9 (9.9)*	101.7 (10.3)*
HR	84.1 (11.2)	96.2 (13.4)*	92.7 (13.5)*
GROUP II (n=30)			
SBP	124.2 (9.8)	135.3 (13.2)	132.9 (9.5)
DBP	78.2 (9.0)	85.6 (14.1)*	85.4 (9.4)*
MBP	92.1 (9.6)	102.1 (12.7)*	101.2 (8.5)*
HR	88.9 (12.3)	100.7 (14.2)*	92.8 (14.1)*
GROUP III (n=30)			
SBP	125.3 (11.7)	127.3 (16.2)	128.3 (13.2)
DBP	77.3 (9.6)	83.4 (14.9)*	81.7 (13.5)*
MBP	93.4 (8.3)	98.0 (14.0)*	97.2 (12.7)*
HR	86.9 (14.4)	96.7 (14.1)*	90.4 (12.3)
GROUP IV (n=30)			
SBP	120.5 (10.4)	131.8 (14.0)*	137.0 (15.0)*
DBP	75.3 (8.8)	87.3 (11.0)*	86.7 (9.6)*
MBP	90.4 (8.5)	102.0 (11.0)*	103.6 (10.7)*
HR	85.1 (8.8)	95.2 (16.3)*	90.0 (14.1)*

*Differed significantly from baseline values ($p < 0.05$)

Title: SAFETY AND EFFICACY OF MIVACURIUM FOR ENDOTRACHEAL INTUBATION

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Introduction: Mivacurium is a short duration nondepolarizing neuromuscular blocking agent currently undergoing clinical trials in the United States. Safety and efficacy of mivacurium to induce neuromuscular block (NMB) for endotracheal intubation were studied in 63 patients undergoing elective surgery requiring general anesthesia. Patients were ASA physical status I or II ranging in age from 18-70 years weighing 45-110 kg. The study was approved by the institutions Clinical Studies Committee, and all patients gave written informed consent.

Methods: Premedication was optional at the discretion of the anesthesiologist and when given consisted of a narcotic and/or a benzodiazepine. Monitoring consisted of blood pressure by automated cuff, heart rate, continuous EKG, oxygen saturation, and axillary temperature. Train of four (T4) responses to supramaximal ulnar nerve stimulation were recorded every 20 seconds by electromyography (EMG) via surface electrodes on the hand (NMT-221, Puritan-Bennett Corp.). Anesthesia was induced with thiopental and fentanyl, and patients were ventilated with O_2/N_2O (50:50) via a semiclosed circle system with bag and mask. After not less than 2 minutes of baseline recording of the EMG, one of 3 doses of mivacurium was administered I.V. The 63 patients were randomly divided into seven groups of 9 each. The dose, method of administration, and time to intubation attempt were varied as shown in Table 1.

Table 1: Study Design

Subgroup	N	Dose (mg/kg)	Method of Admin	Time to Intubation
A1	9	0.15	rapid bolus	2.0
A2	9	0.15	rapid bolus	2.5
B1	9	0.20	rapid bolus	2.0
B2	9	0.20	rapid bolus	2.5
B3	9	0.20	slow(30 sec)	2.0
C1	9	0.25	Rapid bolus	2.0
C2	9	0.25	slow(30 sec)	2.0

Intubation efficacy was evaluated by grading the conditions as follows: 1 = excellent (no cord movement and no cough); 2 = good (no cord movement but slight cough); 3 = fair (cord movement and/or vigorous cough); 4 = poor (not able to intubate). Safety was evaluated by recording vital signs every minute for 10 minutes following intubation and observing closely for clinical signs of histamine release (skin flushing, audible wheezing). Following intubation anesthesia was maintained with 0.5-1.5% inspired isoflurane in N_2O/O_2 (60:40). Recovery of neuromuscular function was documented by $T4 > 0.75$, and residual block was antagonized when clinically indicated. Patients were observed for a minimum of 90 minutes in the recovery room with clinical assessment of muscle strength performed at 20-30 minute intervals. Data were analyzed by ANOVA or paired t-tests when indicated. Intubation scores were analyzed by chi square. Differences were considered significant at $p < .05$.

Results: After analysis of neuromuscular data revealed no statistical differences between subgroups for time to maximum block or block at intubation due either to method of administration or time to intubation, subgroups given the same dose were combined for further analysis. There was no significant difference between groups with regard to doses of anesthetic agents administered prior to intubation. Neuromuscular data as a function of time from injection of mivacurium are shown in Table 2. Depth of block and intubation scores at the initial intubation attempt are shown in Table 3. Sixty of 63 (95%) patients were successfully intubated on the first attempt without administering additional mivacurium. The efficacy of intubation in the 60 patients intubated on the first attempt was not related to dose or depth of block at intubation($p=.54$). Nineteen of 63 patients (30.2%) exhibited mild flushing shortly after administration of mivacurium; however, the incidence of flushing was not related to dose (A=33.3%, B=29.6%, C=27.8%) or method of administration. Hemodynamic changes were judged clinically insignificant at all dose levels. 81% of the patients recovered neuromuscular function spontaneously without need for antagonism of residual NMB. The rest had residual NMB readily antagonized with neostigmine and glycopyrolate. No patients exhibited evidence of recurarization in the recovery room.

Table 2: Neuromuscular Data

Grp	N	Dose (mg/kg)	Time to Max Blk	Max Blk(%)	Time to Beg Rec	Time to 95% Rec	Spont Rec-T
A	18	0.15	4.8	89.4	7.4	21.4	14.3
			(1.6)	(13.8)	(2.0)	(7.1)	(5.8)
B	25	0.20	4.5	97.2	9.9	25.8	16.4
			(1.3)	(6.0)	(3.8)	(6.8)	(4.2)
C	18	0.25	3.3	99.3	12.0	30.9	19.1
			(0.9)	(2.2)	(3.9)	(8.0)	(5.4)

Table 3: Intubation Data

Group	Time to Intub(min.)	Blk at Intub(%)	Score at Intubation 1	2	3	4
A	2.0-2.6	64.8±25.8	8	8	1	1
B	2.0-3.0	72.7±20.5	11	13	1	0
C	2.0-3.0	87.7±18.5	11	5	0	2

Conclusion: Mivacurium is a potent neuromuscular blocking agent which provides good to excellent intubating conditions at 2 to 3 min in a high percentage of patients. The neuromuscular response we measured showed less depression for a given dose then described by Savarese el al.[1] Our recovery data suggests a slight cumulative effect at higher doses which also differs from the results of Savarese. These differences may be due to differences between the EMG response and the mechanical twitch response measured in their study. Although the neuromuscular variables exhibited a dose-response relationship, the intubating conditions were not improved by increasing the dose from 0.15 to 0.25 mg/kg. Due to its short duration of action and rapid rate of spontaneous recovery, the need for antagonism of mivacurium appears to be less than required with longer duration relaxants.

Ref: Savarese JJ et al: Anesthesiology 68:723-732, 1988

TITLE:
PURE OPIATE VS OPIATE VOLATILE ANESTHESIA FOR CORONARY BYPASS SURGERY

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INTRODUCTION

After an opioid induction many cardiac anesthesiologists use a volatile agent to treat or prevent hypertension associated with stressful stimuli during coronary artery bypass grafting (CABG). Concern has been expressed, however, that isoflurane may promote ischemia in the presence of collateral dependent coronary beds.[1] As there have been no randomized trials comparing opiate vs inhalation agent techniques in this circumstance, this study was designed to determine whether the use of isoflurane, enflurane or sufentanil as a supplement to a sufentanil induction affects the hemodynamic stability and incidence of prebypass myocardial ischemia (PBI).

METHODS

With Ethics Committee approval 36 patients scheduled for elective CABG surgery with LVEF$>$40% were studied. Patients were premedicated with morphine, diazepam, scopolamine, and their usual cardiac medication. A continuously recording two channel Holter ECG monitor (mod V5,II) was placed preoperatively followed by standard invasive monitoring line insertions.

Patients were randomly assigned to one of three groups: Group 1 (sufentanil-isoflurane), Group 2 (sufentanil-enflurane), Group 3 (sufentanil). A blinded anesthetic agent vaporizer and 3cc syringes containing either sufentanil 1 ug/kg or normal saline were provided. Patients in groups 1 and 2 (isoflurane and enflurane) had normal saline in the syringes and patients in group 3 (sufentanil) had an empty vaporizer. Anesthesia was induced with sufentanil 5 ug/kg and pancuronium 0.15 mg/kg.

After induction, when systolic BP was $>$15% above average ward values, the vaporizer was opened to 2% and the contents of one 3 cc syringe given. If this intervention failed to return SBP within the required range by 3 min, the vaporizer setting was increased and additional 3 cc syringes were given according to a protocol until systolic BP was controlled or a maximum vaporizer setting of 5% was attained and a total dose of sufentanil 20 ug/kg given. If BP exceeded 30% above ward values a more rapid protocol of increasing vaporizer settings and sufentanil increments was followed. Hypertension (HTN) not controlled by this regimen was treated with nitroglycerin (NTG). ECG and/or pulmonary artery waveform changes suggestive of ischemia were also treated with NTG.

In addition to the Holter tapes and a continuous BP record, hemodynamic profiles were recorded at standard times. End-tidal concentration of the inhaled agent was recorded (mass spectrometer) and "MAC minutes"[2] were calculated. The Holter tapes were analyzed by a cardiologist blinded to the anaesthetic technique. Statistical analysis was performed using ANOVA with students "t" test and chi-square analysis.

RESULTS

There were no significant differences in demographics or hemodynamics between groups. There were four episodes of PBI (Table). One patient in Group 1 became ischemic during induction with stable hemodynamics. The patient in Group 2 became ischemic during intubation simultaneous with increases in BP and HR. One patient in group 3 was ischemic post-intubation with normal hemodynamics. One other patient in this group became ischemic during induction at a time of increased BP, failed all treatment interventions and subsequently responded to NTG. Seven patients out of 14 in Group 3 required NTG for HTN control, and there was a trend to more events requiring treatment in this group. The dose of inhalational agent (MAC min/hr) was similar between the isoflurane and enflurane groups; the mean dose of the opioid in the sufentanil group (including induction dose) was 10.7+1.3 ug/kg.

DISCUSSION

Similar to previous findings pure opiate anesthesia failed to control HTN in 50% of patients.[3] This contrasts to the opiate-volatile technique where hemodynamic control always was established without NTG. Although patients receiving pure opiate had a low incidence of ischemia, hypertension and tachycardia have been associated with an increased risk of PBI,[4] suggesting a "smoother" prebypass course may be of benefit.

These preliminary findings suggest that enflurane or isoflurane can be used with equal efficacy to treat HTN and be associated with an equally low incidence of PBI following 5 ug/kg sufentanil for CABG. While less efficacious for HTN, sufentanil increments result in a similar low incidence of PBI.

Table COMPARISON OF GROUPS

Group (n)	Iso (9)	Enf (13)	Suf (14)
Ischemic Events	1	1	2
Rx Episodes/Pt	4.5+.73	5.0+.08	8.0+3.7
MAC MIN/hr	9.9+1.9	9.1+1.4	
Rx failures	0	0	7*

mean±SEM * $p<0.05$ Rx= treatment; Pt= patient

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Title: HYPERDYNAMIC CIRCULATORY STATE AND BLOOD USE DURING ORTHOTOPIC LIVER TRANSPLANTATION

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Introduction. Patients undergoing orthotopic liver transplantation (OLT) usually have changes in the hepatic and splanchnic vasculature associated with increased portal venous pressure, development of collateral circulation bypassing the liver, and decreased hepatic blood flow. They may also have significant hemodynamic changes with increased cardiac output (CO) and heart rate and decreased systemic vascular resistance (SVR).[1] Associated with this hyperdynamic circulatory state (HCS) is an increased total blood volume, a large portal systemic collateral circulation and low serum albumin levels.[1] It has been postulated that the degree of liver failure may be partially responsible for the HCS. Patients with advanced cirrhosis have a higher cardiac index (CI), lower SVR, and higher azygos blood flow than patients with less advanced disease.[2] The Child's classification, which grades an estimate of hepatic functional reserve, has been used to determine the severity of liver disease[3] and has been utilized for predicting prognosis after portal venous shunt surgery in cirrhotic patients. This study was designed to determine the role of severity of liver disease estimated by Child's class and the presence of HCS on the blood requirements during OLT.

Method. This retrospective review was approved by the Institutional Review Board. One hundred consecutive patients scheduled for OLT who had hemodynamic monitoring were studied (age range 14 to 60 years). The distribution according to diagnosis was cryptogenic cirrhosis (CC) 30, primary biliary cirrhosis (PBC) 26, and primary sclerosing cholangitis (PSC) 27, and miscellaneous 17. All received isoflurane, fentanyl, oxygen, air anesthesia. Preoperative data collected were age, height, weight, degree of encephalopathy, degree of ascites, bilirubin, albumin, and prothrombin time. A Child's class was calculated on each patient. After induction of anesthesia, the mean arterial blood pressure, central venous pressure, and CO by thermodilution technique were obtained. CI and SVR were calculated according to standard formula. Total number of red blood cell units transfused were recorded. HCS was defined as $CI > 3.0$ L/min and a $SVR < 900$ dynes · sec · cm^{-5} using Stevens et al. criteria for normal values under isoflurane anesthesia.[4] Statistical analysis of demographic, clinical, hemodynamic factors on the intraoperative blood requirements were done by two sample T-tests for comparison of means in two groups, and with analysis of variance for comparisons of means in more than two groups. Pearson's correlation coefficients were used to assess the association of age with blood use. Because the blood use distribution was highly skewed, the natural logarithm of the units of blood given was used instead of the actual number of units. $P < 0.05$ was considered significant.

Results. We observed the presence of HCS was associated with higher intraoperative blood use (HCS versus non-HCS = 22.5 mean blood units versus 15.2 mean blood units, $p < 0.01$). There was a positive correlation between the patient's age and the intraoperative blood use (correlation coefficient = 0.26, $p < 0.01$). Patients with Child's C class had a significantly higher intraoperative blood use when compared to patients with Child's class A and B. Child's class C versus B versus A = 29.1 mean blood units versus 16.5 mean blood units versus 13.4 mean blood units ($p < 0.01$). No specific diagnostic category (CC, PBC, PSC) was associated with higher intraoperative blood use.

Discussion. The analysis of our data has identified three distinct independent factors associated with significantly higher intraoperative blood use (presence of HCS, older age, and Child's C class). We found no difference between CC, PBC, and PSC in the amount of intraoperative blood required. HCS has been found to be associated with extrahepatic portal-systemic shunting[5] and these shunts become more evident during the clinical course of cirrhosis with the associated changes in the microvascular bed of the cirrhotic liver.[6] It is likely that any surgical procedure in this subset of patients would be associated with more technical difficulties, impaired hemostasis, and greater operating time. Patients that belong to Child's C class have more pronounced impairment of hepatic function and therefore more serious deficiencies of clotting factors synthesized by the liver. The factors contributing to higher blood use among older patients remains speculative.

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Title: Flumazenil (RO15-1788) Reversal of Midazolam Lacks Adrenergic, Hemodynamic, and Anxiogenic Response

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Introduction. Flumazenil (RO15-1788) is a specific benzodiazepine antagonist acting on central nervous system receptor sites. Intolerable anxiety has been associated with flumazenil reversal of benzodiazepines following surgery (1). We therefore examined the adrenergic, hemodynamic, and anxiogenic response to reversal of midazolam sedation with a titrated dose of flumazenil in postoperative patients.

Methods. Thirty ASA class I and II male patients scheduled for elective surgery under general anesthesia consented to enter this Institutional Review Board approved protocol. The day before surgery each patient had a physical and psychomotor evaluation. Vital signs were recorded. None had a diagnosed psychiatric illness. On the day of surgery an intravenous catheter was inserted for medication and an arterial line was inserted in a radial artery for blood pressure measurements and blood samples. All patients had a midazolam induction. General anesthesia was maintained with 70% nitrous oxide -30% oxygen, fentanyl (0.005 mg/kg/hr or less), midazolam, and isoflurane only if needed. Additional midazolam was given toward the end of surgery to maintain deep sedation and amnesia. On arrival in the recovery room vital signs and psychomotor evaluations were recorded. Arterial blood samples for catecholamine and midazolam concentrations were obtained and placed on ice. In a randomized double-blind fashion patients were then given the intravenous test drug, either placebo or 0.2 mg flumazenil, at 60 second intervals until the patient's sedation was reversed or five doses of test drug had been given. The maximum dose of flumazenil was 1 mg given over 5 minutes; the minimum dose was 0.8 mg. Five, fifteen, and thirty minutes after test drug was begun arterial blood samples, vital signs, and psychomotor evaluations were repeated. The recovery of each patient was observed and evaluated for at least 3 hours after the test drug was given. Arterial serum catecholamines were determined by high pressure liquid chromatography. Results were tested for statistical significance by analysis of variance for repeated measurements, and multiple pair-wise comparisons were made between groups with the Bonferroni t-test.

Results. The flumazenil and placebo groups were demographically similar. All patients were deeply sedated on arrival in the recovery room. Mean arterial midazolam serum concentration was 201 nanograms/ml in the flumazenil group and 168 nanograms/ml in the placebo group. Five minutes after the test drug was begun all of the flumazenil group were awake and talking. The placebo group remained sedated. All patients in both groups had complete amnesia of the surgery and transport to recovery room. None of the patients experienced anxiety following IV flumazenil. There was no statistically significant change in catecholamine or hemodynamic measurements following flumazenil antagonism of midazolam sedation.

Discussion. Reversal of profound midazolam sedation with titrated doses of flumazenil was not associated with a statistically significant adrenergic, hemodynamic, or anxious response. Mental stress causes an increase in arterial catecholamine levels (2) not detected in peripheral venous blood. Therefore, arterial blood catecholamine levels were determined. The reported anxiety of post-surgical patients following reversal of midazolam with flumazenil (1) may have been due to a standard dose given too rapidly (i.e. 0.1 mg/kg over 30 seconds). When flumazenil is titrated to the desired clinical effect at the rate of 0.2 mg/min there was no statistically significant adrenergic, hemodynamic, or anxiogenic response to reversal of profound midazolam sedation.

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Table 1. Flumazenil Group (n=20)

	Sedated	5 min	15 min	30 min
Rf (per min)	19±0.9	19±0.4	20±0.7	19±0.4
HR (per min)	84±4	84±4	85±4	80±4
MAP (mm Hg)	99±5	101±5	102±6	104±5
MIDZ (ng/ml)	201±36	178±37	157±25	146±25
NE (pg/ml)	240±72	308±111	425±153	477±182
EPI (pg/ml)	168±62	230±77	234±82	197±89

Table 2. Placebo Group (n=10)

	Sedated	5 min	15 min	30 min
Rf (per min)	18±0.8	19±0.8	19±0.9	19±0.7
HR (per min)	84±3	82±4	78±4	75±4
MAP (mm Hg)	94±4	96±4	92±4	92±4
MIDZ (ng/ml)	168±25	129±19	120±17	92±12
NE (pg/ml)	176±27	157±25	157±31	129±22
EPI (pg/ml)	48±13	58±14	55±15	50±15

$\bar{X}$±SEM, Rf=respiratory frequency, HR=heart rate, MAP=mean arterial pressure, MIDZ=midazolam, NE= norepinepherine, EPI=epinepherin

TITLE: STABILITY OF CEREBRAL METABOLIC RATE DURING HYPOTHERMIC CARDIOPULMONARY BYPASS IN HUMANS

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Introduction: Cerebral blood flow (CBF) has been reported to decline progressively during stable, hypothermic, nonpulsatile cardiopulmonary bypass (CPB) (1). Possible mechanisms include: 1) a decrease in cerebral metabolic rate for oxygen ($CMRO_2$); 2) cerebral microcirculatory obstruction (2); and 3) pathologic vasoconstriction. Reduced CBF may contribute to the high rate of neurologic dysfunction following CPB (3). This study was designed to confirm a time-dependent decline in CBF during CPB by assessing whether cerebrovascular responsiveness to $PaCO_2$ varies with the direction of $PaCO_2$ change.

Methods: After approval by the IRB, 13 patients scheduled for elective coronary artery bypass grafting (CABG) were enrolled and gave informed written consent. Following premedication with lorazepam and morphine, patients were anesthetized with fentanyl 75 mcg/kg, paralyzed with pancuronium 0.1 mg/kg, intubated and mechanically ventilated. In all patients, nonpulsatile CPB was initiated using a membrane oxygenator, arterial line filter, moderate hypothermia (26-28°C), and α-stat pH management. Patients received two CBF studies, once nasopharyngeal temperature was stable. Either $PaCO_2$ was increased ≈8 mmHg following the first CBF measurement (n=6), or it was decreased ≈8 mmHg (n=7); the second measurement was then performed. This experimental design was chosen because a time-dependent effect would accentuate the CBF reduction produced by a decline in $PaCO_2$ and would attenuate the CBF increase produced by a rise in $PaCO_2$. CBF was measured using the clearance of 133-Xenon injected intra-arterially. Cerebral venous blood was sampled for measurement of oxygen tension and saturation ($S_{jv}O_2$) from a retrograde catheter placed in the right internal jugular vein. $CMRO_2$ was estimated as the product of the cerebral arterio-venous oxygen content difference (A-VDO_2) and CBF. Data from the patients in whom $PaCO_2$ was increased during CPB were compared to data from those in whom $PaCO_2$ was decreased using paired t-tests ($p<0.05$ considered significant). All values are expressed as mean ± SD.

Results: Consistent with previous reports, CBF declined during CPB. Patients in whom $PaCO_2$ was increased between measurements had a lesser change in CBF than patients in whom $PaCO_2$ was decreased ($p<0.05$) (Fig. 1). The exaggerated decline in CBF for patients having decreased $PaCO_2$ was associated with a lower $S_{jv}O_2$ at $PaCO_2$ = 36 mmHg than patients having increased $PaCO_2$ ($p<0.05$) (Table). In addition, patients having decreased $PaCO_2$ had a greater percent change in A-VDO_2 than those having increased $PaCO_2$ (Fig. 2). $CMRO_2$ was identical between measurements within each group.

Discussion: These data confirm that CBF declines spontaneously during CPB, thereby modifying the predicted responses of CBF to increases versus decreases in $PaCO_2$. The associated reciprocal changes in A-VDO_2 validate the measurements of flow and indicate that the changes are physiologically important. In addition, these data suggest that the time-related decline is not secondary to a reduction in $CMRO_2$ (as, for instance, would occur with progressive brain cooling), since $CMRO_2$ remained constant throughout. We conclude that CBF declines during nonpulsatile CPB because of vasoconstriction or vascular obstruction. Further studies are necessary to elucidate the mechanism of this phenomenon.

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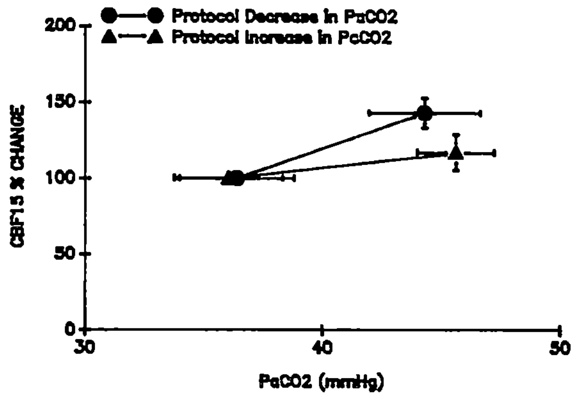

Fig. 1: Percent Change in CBF vs $PaCO_2$

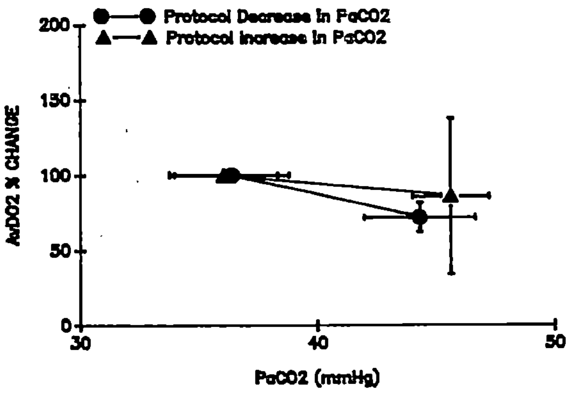

Fig. 2: Percent Change in A-VDO_2 vs $PaCO_2$

	$PaCO_2$ (mmHg)	$CMRO_2$ ($ml \cdot 100g^{-1} \cdot min^{-1}$)	$S_{jv}O_2$ (%)	Hct (Vol%)
$PaCO_2$ decrease	44±2	.46±.09	75± 6	23±3
	36±2	.46±.07	64± 7*	24±4
$PaCO_2$ increase	36±2	.33±.12	77±10*	23±2
	46±2	.33±.17	80±11	24±2

*intergroup difference p<0.05

Title: **CHANGE IN FREQUENCY OF PRE OP TEST ORDERING IN TWO CITIES OVER TIME**

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Introduction. Over the last fifteen years, multiple technology assessments have indicated that routine preoperative screening tests, such as chest x-ray (CXR), electrocardiogram (ECG), prothrombin (PT), partial thromboplastin (PTT), and electrolyte (Lyte) tests may not be beneficial and, in fact, may be harmful because of the iatrogenic disease they engender. For example, between 1973 and 1979, six studies in the American and British literature (1) found no benefit for CXRs in asymptomatic patients under the age of 60. In 1979, a major study sponsored by the Royal College of Radiologists confirmed the absence of benefit from preoperative CXRs in asymptomatic individuals under the age of 60. This lack of benefit was presented at major meetings of the American Society of Anesthesiologists, American College of Surgeons, and North American Society of Radiologists in 1979. In 1983, the FDA published such a conclusion in the Federal Register, and the lack of requirement for CXRs preoperatively was endorsed by all the above named societies by 1984. Since then, other studies showed a similar lack of benefit for preoperative ECGs in asymptomatic individuals under 40, and preoperative PT, PTT, and Lyte tests in asymptomatic individuals.

Yet the impact of these studies and medical society endorsements has not been evaluated. We undertook this study to test the hypothesis that physicians have substantially reduced the ordering of unindicated preoperative tests since 1977.

Methods. After institutional review boards in two different cities approved the study, we reviewed over 1,000 patient medical records including at least 100 from every other year of a ten year period to determine the incidence of indicated and unindicated preoperative CRXs, ECGs, PTs, PTTs, and Lyte panels for different operations. We used the following guidelines in collecting the data: Unindicated CXRs--those ordered for individuals under the age of 60 with no history or symptoms of lung disease, heart disease, or cancer. Unindicated ECGs--those ordered for individuals under the age of 40 with no history or symptoms of heart disease or diseases affecting the circulatory system. Unindicated PT and PTT tests--those ordered for individuals who displayed no history of bleeding diathesis. Unindicated Electrolyte Panels--those ordered for individuals showing no evidence of metabolic disease or drug usage that would affect electrolytes. All tests not in the unindicated categories were defined as indicated. The resulting data were analyzed using chi-squared tests and a test for trend in proportions statistics.

Results. Data from the two cities did not differ, and results from these cities are pooled. The results indicated that ordering of some unindicated tests (e.g., the ECG and CXR for T & A and the CXR for Arthroscopy [Arthros]) has declined substantially, while other unindicated tests (e.g., the PT and PTT for T & A, Arthros and Total Hip Replacement [THR], the CXR for Arthros and THR) has not changed (table 1). In addition, the percentage of indicated tests not ordered has increased substantially.

Discussion. It appears that there has been a substantial reduction of the ordering of some unindicated tests in certain operations. Yet we found no decline in the ordering of other unindicated tests for the same operation, or in the ordering of the same unindicated test for different operations. But physicians, perhaps in their zeal to be cost conscious or to prevent iatrogenic disease, are not obtaining some indicated tests. Since omitted preoperative tests that are indicated may be a greater risk to the patient than extra tests, this is especially disturbing. We conclude that a better system for obtaining indicated tests and for omitting unindicated tests may be a necessary supplement to education and standard endorsements for reducing errors in test selection.

Percent of Patients Receiving
CXR When Indicated

Operation	T&A	Arthros	THR	IHR
1977				100%
1979	100%	ND		100%
1981	33%	100%	100%	100%
1983	33%	50%	100%	86%
1985	ND	0%	91%	60%
1987	ND	0%	100%	
	*	NS	NS	*

Percent of Patients Receiving
ECG When Indicated

Operation	T&A	Arthros	THR	IHR
1977				50%
1979	100%	100%	100%	84%
1981	25%	89%	100%	77%
1983	0%	60%	100%	100%
1985	ND	50%	100%	100%
1987	ND	100%	100%	
	NS	NS	NS	*

Percent of Patients Receiving
CXR When Not Indicated

Operation	T&A	Arthros	THR	IHR
1977				100%
1979	78	85		0%
1981	38	72	100	79%
1983	3	50	100	100%
1985	11	4	75	100%
1987	25	11	100	
	*	*	NS	NS

Percent of Patients Receiving
ECG When Not Indicated

Operation	T&A	Arthros	THR	IHR
1977				100%
1979	0	4	ND	0%
1981	7	4	ND	63%
1983	11	0	ND	84%
1985	11	4	ND	0%
1987	19	22	ND	
	NS	NS		NS

Percent of Patients Receiving PT
&/or PTT Tests When Not Indicated

Operation	T&A	Arthros	THR	IHR
1977				
1979	0	33	100	60
1981	8	6	88	58
1983	18	3	97	43
1985	ND	0	91	87
1987	6	10	100	84
	NS	NS	NS	NS

ND = no data; T & A = tonsillectomy & adenoidectomy; Arthros = arthroscopy; THR = total hip replacement; IHR = inguinal hernia repair; NS = not significant

*$P \leq 0.05$ or greater change over time

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Title: **FACTORS WHICH AFFECT MIDAZOLAM UPTAKE BY THE SCI-MED MEMBRANE OXYGENATOR**

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Introduction. Midazolam is often utilized in patients undergoing cardiac procedures because of its inherent cardiovascular stability. No information is available concerning the pharmacokinetics of midazolam during cardiopulmonary bypass (CPB). Midazolam is a lipid soluble benzodiazepine. Absorption of other lipophillic anesthetic agents by silicon containing membrane oxygenators has been previously documented.[1] The purposes of this study were multiple. First to demonstrate the potential for CPB interaction with midazolam by direct binding to the oxygenator. Second to evaluate the characteristic of this interaction under different temperature conditions and finally to assess the potential for reversibility of midazolam uptake by the oxygenator.

Methods. A midazolam in Normosol-R (pH adjusted to 7.4) solution was prepared with tritiated midazolam. The final concentration of midazolam was 14 mcg/ml. EXPERIMENT 1: Four 1 x 1 cm squares were cut from a Sci-med membrane oxygenator and weighed. Each membrane square was individually placed in a test tube containing 2cc of the midazolam solution.

The test tubes were continuously agitated with a vortex genie mixer. Squares were removed from the solution after one hour and washed with distilled water. Absorption of tritiated midazolam, was detected by liquid scintillation. Two of the sample tubes were incubated at room temperature=23°C. The other two solutions were initially warmed to 37°C then cooled to 30°C during the course of the experiment.

EXPERIMENT 2: Three 1 x 1 cm squares of membrane were placed individually in test tubes containing 2cc of the midazolam solution. After one hour of incubation with agitation at room temperature=23°C, each saturated square was removed from solution and washed with distilled water. 2ml of Normosol-R was then placed in 3 separate test tubes. Control samples were obtained at time 0 and a saturated membrane square was placed in each of these Normosol-R containing tubes. Fluid samples were obtained at .5, 5, 10, 20, 30, 40, 50 and 60 minutes. Liquid and membrane samples were analyzed for midazolam content by liquid scintillation.

Results. EXPERIMENT 1: Binding of midazolam by the sample piece of membrane material was directly demonstrated. There was no significant difference in the amount of midazolam binding which occured during the 2 temperature conditions.

EXPERIMENT 2: The reappearance of midazolam was detected in solution (Figure 1). Equilibrium between membrane bound fraction and free midazolam in solution occured at 30 minutes. The membrane retained 4.6 ± .13 mcg/cm^2 after one hour while the midazolam in solution rose from 0 to 3.9 ± 0.19 mcg.

Discussion. This study is the first to directly measure midazolam absorption on membrane material. Through use of a radiolabelled technique, midazolam which was lost from solution could be demonstrated to be attached to the membrane sample. Many clinically relevant variables may modify the volume or degree of this interaction. These experiments were performed at a clinically relevant pH=7.4. The interaction may be altered with acidosis or alkalosis. Temperature was studied as an independent variable. Initial warming of the solution to 37°C followed by cooling to 30°C attempted to simulate the temperature changes clinically encountered when initiating CPB. There was no significant difference in the amount of midazolam bound to the membrane at room temperature to that detected after temperature increases.

A second clinically important variable is the nature of the midazolam membrane interaction. The binding of midazolam is at least partially reversible. Assuming a mean saturation of 7.4 mcg/cm^2 approximately 2/3 of the bound midazolam is retained after bathing in Normosol for one hour. No further release of midazolam from the membrane was apparent after 30 minutes.

This data suggests that the Sci-med 0400-2A is capable of absorbing at least 29.6 mg of midazolam. The larger Sci-med 3500-2A used for adult CPB is projected to be able to absorb 259 mg of midazolam. However the data also supports the hypothesis that this interaction is reversible and that an equilibrium between membrane and plasma concentrations may be achieved. Many potentially influential variables need to be studied in addition to temperature and pH to more fully understand this phenomenon. This is a clinically relevant issue in patients undergoing CPB. We propose that not only is there a risk of developing subtherapeutic plasma fentanyl concentrations during CPB but also subtherapeutic midazolam levels. Clinical studies will need to be performed to confirm the invivo results of this invitro model.

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FIGURE 1

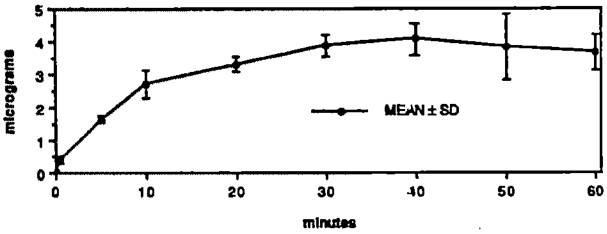

Fig 1: appearance of midazolam in solution

Title: SILENT MYOCARDIAL ISCHEMIA AND VENTRICULAR ECTOPY IN PATIENTS UNDERGOING TURP

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Decreases in hematocrit and increases in intravascular volume, caused by blood loss and the uptake of free water, reduce oxygen carrying capacity and increase myocardial oxygen demand, thereby posing a theoretical risk of myocardial ischemia to elderly men undergoing transurethral resection of the prostate (TURP). Although patients receiving a regional anesthetic for TURP are able to sense angina, sedatives and analgesics administered during the anesthetic could blunt such recognition and render these patients vulnerable to episodes of silent myocardial ischemia. In the perioperative period, the morbidity of silent myocardial ischemia, which is defined as the objective signs of ischemia in the absence of clinical symptoms, is being recognized with increasing frequency. Therefore we undertook a controlled prospective investigation, using continuous ECG (Holter) monitoring, to evaluate the occurrence of silent ischemia in patients having TURPs.

METHODS. Following Human Investigation Committee approval, seventy-six (N=76) patients undergoing urologic procedures in the cystoscopy suite were enrolled in the study. Group I = 29 TURP patients; Group II = 47 non-TURP patients, eg. cystoscopy, bladder fulgerations, etc. Clinical management was at the discretion of the primary anesthesia care team. Preoperative data were collected for: cardiac risk factors (hypertension, prior cardiovascular disease, etc.), hematocrit, electrolytes, ECG, CXR. Upon arrival in the holding area BP cuff, standard OR monitoring ECG (II/V5), and a continuous ECG recorder (Holter) (Marquette 8500 series) were applied. Cardiovascular data were then collected until discharge from the recovery room. In addition, pertinent intraoperative anesthetic information was recorded: technique, drugs, overt ECG abnormalities (eg. ischemic changes or dysrhythmias in II/V5). Patients were then observed during their subsequent hospital course, to a maximum of 48 hours. Post-operative data included ECG, hematocrit, and electrolytes. A Marquette AM Holter ECG monitor appropriately calibrated for the patient in a supine position was used for all patients. Two bi-polar leads, modified V1 and modified V5, were applied according to standard criteria. The continuously recorded ECG tapes were analyzed with a Marquette series 8000 computerized ECG analysis system. Two cardiologists blinded to the patient's clinical course evaluated the reports and appropriate ECG strips. A diagnosis of ischemia was made if there was a $\geq$ 2 mm ST elevation or $\geq$ 1 mm ST depression measured at 80 ms after the J point occurring for at least one minute in one lead of the continuous ECG. The chi square and unpaired t test were used for statistical analyses, with $p < 0.05$ considered significant.

RESULTS. (see Table) Holter recordings were obtained in 76 patients (total 303 hours), with ST analyses readable in 68 patients. No patient in either group demonstrated ischemia on the Holter ECG. All patients were continuously monitored by ECG and no episodes of ischemia were observed on the OR monitors. In contrast to ischemia, a high incidence of ventricular ectopy was noted in both groups. Further analysis, based on age, showed that ventricular ectopy was noted in 72% of the patients older than 60 years, and in only 14% of the younger patients ($p < 0.05$). There were no significant differences in ventricular ectopy when patients older than 60 years were analyzed as: TURP vs non-TURP or as risk factor vs no risk factor present.

TABLE

	I TURP (N=29)	II non-TURP (N=47)	p
age $>$ 60 yr	29 pts	26 pts	NS
$>$ 1 Risk Factor	18 pts	27 pts	NS
Regional Anesth	28 pts	27 pts	NS
Ischemia	0 pts	0 pts	NS

DISCUSSION. In other high risk surgical and medical populations silent ischemia has been observed to be frequent and to be prognostic of a poor outcome (ref 1,2). TURP patients have been regarded as a high risk group because of their advanced age and the electrolyte changes, as well as blood loss and fluid uptake. We conclude that: (1) silent myocardial ischemia is not prevalent in patients undergoing TURP, and (2) ventricular ectopy is related to age and not cardiac risk factors or the TURP procedure.

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Title: ISOTONIC HYPONATREMIA DURING TRANSURETHRAL PROSTATE RESECTION

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Introduction. Acute hyponatremia following intravascular absorption of irrigating solutions is a well described complication of transurethral resection of the prostate (TURP). With the use of osmotically active irrigating solutions, the concomitant intravascular absorption of osmotically active solute occurs, and marked shifts in brain water are thereby attenuated. Indeed, since distilled water has been replaced by these agents, major neurologic sequelae and death are rarely seen due to this complication. Assessment of serum osmolality and calculating the osmolar gap in differentiating acute isotonic hyponatremia from the potentially more critical acute hypotonic hyponatremia in the setting of TURP is a concept described in the nephrologic and urologic literature. This concept, however, is less well described in the anesthesia literature and therefore often overlooked by the anesthesiologists who routinely treat these patients. We report two cases of isotonic hyponatremia as a complication of TURP and emphasize the use of the osmolar gap in correctly diagnosing and treating these patients.

Methods. Two patients, ages 66 and 75 years, presented with signs and symptoms of urinary tract obstruction secondary to benign prostatic hypertrophy. Both patients were being treated for hypertension. The remainder of their histories were unremarkable. Admitting laboratory data was as follows:

	Patient#1	Patient#2
Serum sodium	143 meq/L	141 meq/L
BUN	59 mg%	29 mg%
Serum glucose	95 mg%	100 mg%

Both patients underwent TURP under spinal anesthesia with tetracaine. Minimal sedation was utilized. Saline, 0.9%, was used as maintenance intravenous fluid. Bladder irrigation solution was 1.5% glycine. During the course of the resection perforation of a prostatic venous sinus occurred in both patients. Subsequently, the patients developed confusion, hemodynamic, and EKG changes. Patient #2 manifested signs and symptoms of pulmonary edema, requiring endotracheal intubation. Prior to the institution of any other therapy, laboratory data was obtained with the results as follows:

	Patient#1	Patient#2
Serum sodium	116 meq/L	102 meq/L
Serum glucose	100 mg%	105 mg%
Serum BUN	55 mg%	21 mg%
Measured serum osm.	298 mOsm/kg·H_2O	286 mOsm/kg·H_2O
Calc. serum osm.*	256 mOsm/kg·H_2O	217 mOsm/kg·H_2O
Osmolar gap**	42 mOsm/kg·H_2O	69 mOsm/kg·H_2O

*defined as 2 x serum sodium + glucose/18 + BUN/2.8

**defined as measured serum osmolality - calculated serum osmolality

Results. Both patients were treated with intravenous furosemide. Patient #1 also received 3% saline prior to knowing the results of the osmolar gap. Despite the marked acute hyponatremia both patients experienced no neurologic or cardiac sequelae and were discharged within seven days of their surgery.

Discussion. Extravastion of irrigating solution is a well known complication of TURP (1). However, the introduction of non-hemolytic irrigating solutions has essentially eliminated the problem of intravascular hemolysis during TURP. These solutions, however, are for the most part hypotonic and despite eliminating hemolysis, intravascular absorption of these solutions may lead to acute profound hyponatremia. Major neurologic sequelae during TURP have been felt to be due to this rapid decrease in serum sodium. A debate remains in the literature regarding the incidence, pathophysiology, and treatment of the TURP syndrome. However, attributing symptoms of confusion, seizures, come and death solely to acute hyponatremia induced cerebral edema does not appear to be fully warranted. The key to interpreting these neurological changes depends upon differentiating hypotonic hyponatremia from isotonic hyponatremia utilizing the osmolar gap (2). When the measured serum osmolality exceeds the calculated osmolality by greater than 10 mOsm/kg·H_2O, an increased osmolar gap exists. This implies unmeasured solute must be present in plasma water in significant amounts, and therefore may influence net movement of water across cells. Substances such as glycine, mannitol or sorbitol, all agents used as irrigating solutions during TURP, are relatively impermeant. Accumulation of these solutes in the plasma, as seen during prostatic sinus perforation, will therefore influence tonicity and net transcellular water movement. With the brain responding like an osmometer, intracellular swelling or shrinking is dependent upon decreased or increased effective plasma osmolality. Provided that a relatively normal effective osmolality is maintained, cerebral edema should not occur. In both patients reported, a significant amount of osmotically active glycine was also simultaneously absorbed, generating a marked osmolar gap. It is important to note that serum osmolality remained near normal despite severe hyponatremia and that the neurologic changes that occurred, may have been due to hypoxemia, ammonia toxicity, or possibly due to cation induced alterations in glial transmembrane potential, but it is very unlikely to be due to acute cerebral edema. These patients represent a classification of hyponatremia best characterized as isotonic hyponatremia. Patients who develop acute symptomatic hyponatremia with hypotonicity carry a near 50% mortality (3). Our patients, and the reported patients who suffer hyponatremia during TURP, have a mortality of less than 1%. This appears to be directly related to maintenance of near normal effective osmolality by absorption of an osmotically active irrigating solution. Treatment of patients with isotonic hyponatremia with hypertonic saline may lead to a more life-threatening hyperosmolar state, also associated with well documented morbidity and mortality (4). In contrast, if significant fluid absorption occurs without concomittant absorption of an osmotically active agent, hypotonicity will ensue and intracellular cerebral edema with seizures, coma and death may all be possible. It is these patients only, in the absence of pulmonary edema, in which treatment with hypertonic saline is indicated.

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Title: **DETERMINATION OF ARTERIAL-ENDTIDAL CO$_2$ GRADIENTS: EFFECTS OF POSTOPERATIVE CARDIORESPIRATORY SUPPORT**

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Introduction. Continuous measurement of end-tidal carbon dioxide (EtCO$_2$) by mass spectrometry and infra-red capnometry is routinely utilized to monitor ventilation and follow trends of arterial carbon dioxide (PaCO$_2$) in anesthesized patients. The PaCO$_2$-EtCO$_2$ gradient (previously documented as 4.24 ± 4.42* mmHg) has been demonstrated to vary but the initial and subsequent differences correlate significantly.[1] This allows the EtCO$_2$ to be used as an indication of PaCO$_2$ or changes in PaCO$_2$ during mechanical ventilation (IMV) in the intensive care unit (ICU).[2] The gradient, which is determined by respiratory deadspace (VD/VT) and venous admixture, may be affected by respiratory and circulatory changes that effect these variables.[3] The effect of decreasing ventilatory support during IMV weaning, therapeutic infusion of vasoactive agents, and the associated changing hemodynamic parameters on the PaCO$_2$-EtCO$_2$ gradient was evaluated in postoperative cardiac surgery patients.

Method. After approval of the Hospital Human Studies Committee, 23 patients (20 male, 3 female) aged 62±9 (41-75 yr**) were studied after cardiac surgery (18 CABG, 3 value replacement, 1 both and 1 transplant). All patients were monitored by EKG, intra-arterial pressure, pulmonary artery pressure, EtCO$_2$, arterial blood gases and thermodilution cardiac outputs. EtCO$_2$ was measured by the Hewlett Packard 78520A infra-red capnometer. The PaCO$_2$-EtCO$_2$ gradient was followed from the postoperative ICU admission with full mechanical ventilation to extubation. Gradient comparisons were made during IMV weaning at different ventilator rates, and at different levels of FiO$_2$, cardiac output and index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), pulmonary capillary wedge pressure (PCWP) and during infusions of nitroglycerin (NG), nitroprusside (NP) dopamine (DP), dobutamine (DB) and aramine (AR). Data was analyzed by Student t-tests or analysis of variance with $p < 0.05$ considered significant.

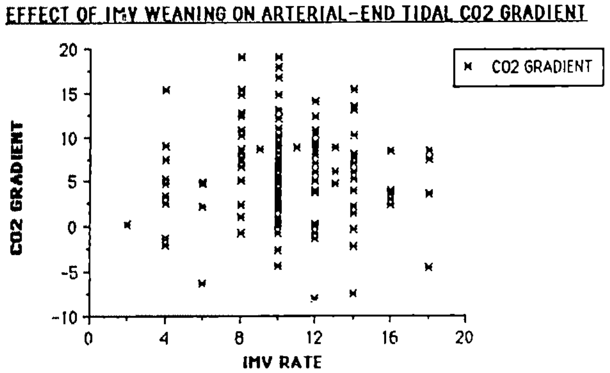
Results. The mean PaCO$_2$-EtCO$_2$ graditent was 5.47±5.21 mmHg (PaCO$_2$ mean 36.51±5.89, EtCO$_2$ mean 31.04±6.44). The correlation was significant (R 0.644, $p < 0.0001$) throughout stabilization, IMV weaning and drug infusion changes. There was no significant correlation between the PaCO$_2$-EtCO$_2$ gradient and wide ranges of ventilator rate (0-18 breathes per min.), FiO$_2$ (0.4-1.0), CI (1.7-42 $l \cdot min^{-1} \cdot m^2$), PCWP (6-30 mmHg), SVR (700-2150 dynes/sec cm^5), and PVR (105-265 dynes/sec cm^5). There was no correlation between PaCO$_2$-EtCO$_2$ gradients and infusions of NP (52 observations, 0.17-7.8 $ug \cdot kg^{-1} \cdot min^{-1}$), NG (80 observations, 23-150 $ug \cdot min^{-1}$), dopamine (50 observations, 1-10 $mg \cdot kg^{-1} \cdot min^{-1}$) as well as less frequently evaluated infusions of dobutamine and aramine.

Discussion. PaCO$_2$ and EtCO$_2$ correlate significantly in postoperative patients who have had major cardiac surgery. The correlation extends through IMV weaning to total spontaneous ventilation (SV), with varying inspired oxygen concentrations and during varying hemodynamic status and pharmacologic manipulation. Factors that might have been expected to affect the PaCO$_2$-EtCO$_2$ gradient through altered ventilation-perfusion homogeneity (CI, PVR, SVR, and PCWP) and/or increased venous admixture (PVR, NP, NG, and DB infusions) did not. There was also no correlation with age which has been previously shown. The change from full IMV support to SV or the ventilation-perfusion mismatch that is present after postcardiotomy and its presumed changing status did not affect the gradient (Fig. 1).

Conclusions. The PaCO$_2$-EtCO$_2$ gradient, although varying in degree, maintains a significant correlation between the two measurements throughout IMV weaning in postoperative cardiac patients. The inotropic, vasopressor and vasodilater agents evaluated during this period and their effects on myocardial contractility, vascular reactivity and hemodynamic variables also did not produce significant effects.

* values as mean ± S.D.

** values as ranges



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Title: REAL-TIME EVALUATION OF SEGMENTAL WALL MOTION ABNORMALITIES

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Introduction. Myocardial ischemia occurs during surgery in patients with coronary-artery disease, and transesophageal echocardiography (TEE) more reliably detects ischemia than multilead ECG (1). However, previous studies have not tested the validity of real-time evaluations of echocardiograms, but, instead, employed postoperative evaluations by multiple observers. The goal of the current study is to evaluate the validity of real time interpretation of TEE during surgery.

Methods. After approval of our Human Research Committee, we studied 13 patients undergoing vascular or cardiac surgery. The left ventricular short-axis images were arbitrarily divided into four segments (inferior, posterior, anterior and septal) by imaginary lines passing through the antero-lateral and postero-medial papillary muscles. The grading system was defined as follows: 1 = normal wall motion: shortening >30% of the imaginary radius and normal thickening; 2 = mild hypokinesia: shortening from 10-30% and slightly reduced thickening; 3 = severe hypokinesia: <10% shortening and minimal thickening; 4 = akinesia: no shortening and no thickening; 5 = dyskinesia: lengthening and wall thinning. A worsening of >2 classes indicated ischemia. After the patients were anesthetized, an independent operator inserted the esophageal probe (phased array 5.0 MHz Hewlett Packard, Andover, MA) to produce a short-axis image at the mid-papillary muscle level. Then, the anesthesiologists were briefly trained (1-5 min.) in the identification and analysis of wall motion abnormalities, including the grading system. Readers (resident and faculty anesthesiologists) independently evaluated the segmental wall motion at four different intervals during surgery for all patients. Simultaneously, the short-axis view was recorded on a videotape for subsequent evaluation by two independent, experienced observers. Disagreements between the two experienced observers were arbitrated by a third observer.

Results. We analyzed 168/208 segments. Thirty-six segments were not evaluated because one of the anesthesiologists was unavailable for the real-time evaluation and four segments were inadequately visualized. Residents correctly detected 97.2% (138) of normal wall motion (grade <3), and faculty members, 98.6% (140). Twenty-six segments had abnormal wall motion (grade >2): residents were able to detect 61.5% (16) and faculty members 77% (20) of these. The experienced readers disagreed on 9 segments (normal vs. mildly abnormal wall motion). Three episodes of ischemia occurred; one was detected by the faculty members and none by the residents.

Discussion. Real time evaluation of TEE often fails to identify significant left ventricular segmental wall motion abnormalities (SWMA). More importantly, these preliminary data suggest that even the development of new SWMA (presumably due to ischemia) during the monitoring period can be missed. In retrospect, this result should not be surprising, since previous studies have documented that most ECG changes are also missed by the anesthesiologist (2). Our experienced observers had an unlimited time to evaluate each echocardiogram and our clinicians usually less than 30 sec. Multiple other responsibilities precluded a longer period of evaluation for our clinicians; moreover, they were not provided the opportunity to review the previously recorded episodes for comparison. Finally, many of our participating residents had little experience with TEE (fewer than 5 cases), but lack of experience alone seems a much less likely explanation for their results, because the real time evaluations by the anesthesiologists (more than 50 cases) were not significantly better. We believe changes in segmental wall motion are more easily appreciated when the two images (control and real time) are viewed simultaneously. We are now evaluating this hypothesis.

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Title: EPIDURAL SUFENTANIL IN DOGS: ANALGESIA VERSUS PLASMA CONCENTRATION

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Introduction. Sufentanil has a high μ-receptor affinity and lipid solubility (1). This suggests a drug action which should have a rapid onset and yield a significant spinal analgesic effect (2). In the present study we examined the antinociceptive, and side effects and toxicity of epidural sufentanil in dogs. Sufentanil was daily administered for 15 days. On days 1 and 15, blood samples were taken to correlate the effects of 3 different doses with the plasma levels. This gives the opportunity to study the redistribution in plasma, the correlation of drug levels with the antinociceptive effects and the effect of chronic implantation on drug redistribution.

Methods. The study was approved by the Institutional Animal Care Committee. Beagles (±10 kg 3 males and 3 females in each group), under halothane anesthesia with aseptic procedures, were implanted with epidural catheters (PE-50 tubing), inserted at the L_7/S_1 interspace and passed to the level of L_3/L_4. The catheter was tunneled subcutaneously to exit in the neck. After 3 days of recovery, daily injections of sufentanil were initiated for 15 days. Dogs were randomly assigned to receive a daily epidural dose of 10, 50 or 100 μg in a volume of 2 ml. Each group consisted of 6 dogs. On days 1 and 15, blood samples were taken on certain time intervals (0, 1, 3, 6, 10, 20, 40, 60, 120, 150, 180, 240, 300 min). Neurological and nociceptive characteristics were followed during the same time. The nociceptive response was quantitated by measuring the response latency of the thermally evoked skin twitch produced by applying a thermal probe (70°C) to the flanks. At sacrifice, dogs were perfused and histopathology examined.

Results. While there was significant inter-animal variability (e.g. as much as 2-fold in peak plasma levels), the peak concentrations were always in the first 6 min after injection for all the groups on days 1 and 15. A clear antinociceptive effect at that moment was always seen. The values and SEM of the plasma AUC of the time (300 min) concentration (ng/ml) curve are listed in the following table (min • ng/ml).

	10 μg	50 μg	100 μg
Day 1	66.5 (±19)	83.6 (±13.7)	133.3 (±47.5)
Day 15	107.4 (±44.9)	66.1 (±22.2)	120.3 (±34.0)

There is no statistical difference in the plasma concentration-AUC between days 1 and 15 at any drug dose. As shown in Figure 1, however, the plasma concentration during the first 60 min are much higher on day 1, suggesting a more rapid absorption into blood. While a rapid onset of antinociception was observed at this dose on days 1 and 15, there was a moderate attenuation of the antinociceptive AUC and peak drug effect (MPE) over this time interval, suggesting tolerance. Similar results were observed with the lower doses (data not shown). Upon sacrifice, examination of the spinal cord revealed that around all catheters (including 6 control dogs) that there was a prominent organization of the epidural fat, which visably modified the redistribution of dye injected at the time of sacrifice. This barrier provides a possible explanation for the slower drug absorption in the plasma. The microscopic and macroscopic examination of the spinal cord gave no evidence of any hemorrhage or inflammatory reaction at any dose.

Discussion. The plasma absorption of epidurally injected sufentanil in dogs is rapid and significant. Besides the spinal action, the analgesic effect appeared due in part to a central effect, even at the lowest dose of 10 μg (1 μg/kg). The side effects we observed (behavior depression, respiratory bradycardia, etc.) correlated well with the plasma concentration. Over the 15 days, tolerance development was seen. The tissue organization around the catheter in the epidural space can be an explanation for the slower plasma absorption on day 15. These studies further emphasize the lack of neurotoxicity of sufentanil even at high concentrations.

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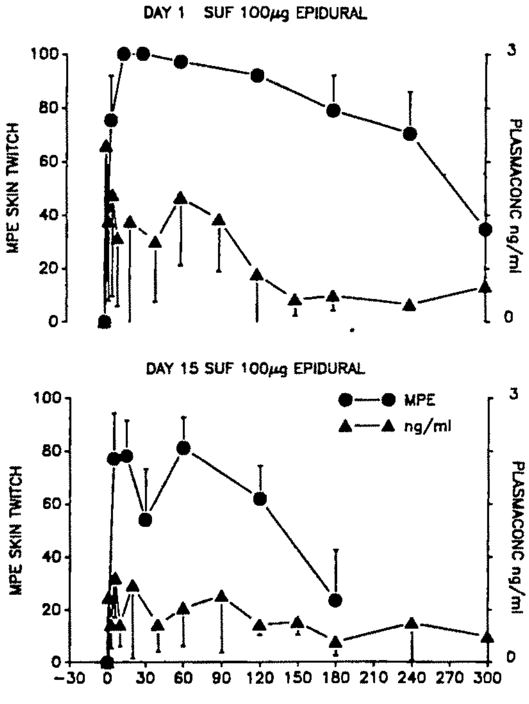

Figure shows nociception expressed as maximal possible effect of the skin twitch (MPE) and plasma concentration (ng/ml) versus time on days 1 and 15 for 100 μg epidural sufentanil in dogs.

Title: THE EFFECTS OF SUCCINYLCHOLINE ON THE MASSETER MUSCLE TONE OF STRABISMUS PATIENTS

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Introduction. Patients undergoing strabismus surgery who receive halothane and succinylcholine during anesthesia are reported to have an increased incidence of masseter muscle rigidity (MMR)[1]. This "masseter spasm" is recognized as a valuable early sign of malignant hyperpyrexia (MH). Succinylcholine has been found to routinely increase jaw muscle tone during halothane anesthesia[2]. This study was undertaken to investigate (i) the increased resting tension of the masseter muscle in patients with strabismus, (ii) the time course of this effect and (iii) its relationship to maximum twitch depression, and these parameters were compared with a non-strabismus control group.

Methods. Sixteen patients aged 3-10 years taking no medications were studied following institional approval and informed parental consent. The patients were ASA I, unpremedicated and scheduled for elective day care surgery requiring general anesthesia with endotracheal intubation. Eight patients were undergoing strabismus surgery and eight patients in the control group were undergoing dental or E.N.T. procedures. Patients with neuromuscular disease or abnormalities of jaw opening were excluded. Anesthesia was induced with halothane, N_2O (66%) and O_2 (34%) and atropine 0.01 $mg.kg^{-1}$ administered intravenously. Endotracheal intubation was performed under deep halothane anesthesia. Skin electrodes were placed below each zygomatic arch, anterior to the mandibular condyles in close proximity to the nerve supplying the masseter. A force transducer system was attached to a securely taped oral airway and to a metal frame fixed to the operating table[3]. Supramaximal train of four stimuli were applied every 12 seconds to the ulnar nerve and the nerve to masseter and the evoked twitch response was recorded. Succinylcholine, 1.0 $mg.kg^{-1}$, was given and a recording continued until full recovery occurred for both muscles. Baseline increases in resting tone were measured in grams. Time to onset, maximum effect and duration of effect for resting tension increase and twitch depression were measured for both muscles and were compared by paired Student's "t" test.

Results. There were no significant differences between the control and strabismus groups with respect to age, weight and height. Although there were no significant differences between the two groups for onset time, time to maximum tension, duration of effect or maximum tension generated, (Table I) all these parameters were greater in the strabismus group. Maximum neuromuscular block for the strabismus group was 97.6% ± 1.5% at the adductor pollicis and 100% ± 0% at the masseter muscle and occurred within 72 ± 11 s and 30.8 ± 3.2 s respectively. Maximum resting tension increases occurred during maximum twitch depression. Duration of twitch depression was 301 ± 21 s and 323 ± 19 s for the strabismus and control groups respectively.

Discussion. This study confirms that there is a consistent but variable increase in the tone of the jaw muscles following clinically used doses of succinylcholine. However, the results do not demonstrate a significant difference in this increase in resting tension between strabismus and control patients. The duration of the increased tone is comparable to that of MMR and may represent a subclinical form of this condition. The phenomenon occurs during maximum twitch depression and could be due to a direct action of succinylcholine on masseter muscle.

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TABLE I

Time relationships of increased resting tensions of masseter for both groups and maximum tension observed. Mean values in seconds ± SEM and grams ± SEM.

	STRABISMUS	CONTROL
Onset Time Seconds	12.4 ± 2.9	9.3 ± 3.0
Time to Max Tension Increase	38.6 ± 3.8	31.0 ± 2.2
Duration In Seconds	134.9 ± 30.3	74.1 ± 21.4
Maximum Tension In Grams	55.7 ± 8.2	45.3 ± 11.8

Title: POTENCY OF ATRACURIUM ON MASSETER AND ADDUCTOR POLLICIS MUSCLES IN CHILDREN

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Introduction. Upper airway muscles help to maintain the integrity of the breathing passages and require adequate relaxation before intubation can be performed. The masseter, a muscle which closes the jaw, is an important member of this upper airway group. This study was designed to evaluate the potency of atracurium on the masseter and adductor pollicis muscles in children.

Methods. After institutional approval and informed parental consent, ten children aged between 3-10 years scheduled for elective surgery were studied. Routine monitoring consisted of dinamap, electrocardiogram, nasopharyngeal temperature and precordial stethoscope. Anesthesia was induced by mask or with thiopentone 3-5 mg.kg^{-1}, and N_2O (66%) and O_2 (34%) and progressively higher concentrations of halothane were administered until intubation could be accomplished without the use of muscle relaxants. After intubation, the inspired halothane concentration was set at 1% and ventilation was controlled to maintain normocapnia. Supramaximal train of four stimulation was applied to the ulnar nerve at the elbow and to the nerve to the masseter, which originates from the mandibular branch of the trigeminal nerve below the zygomatic arch, anterior to the mandibular condyles. A force transducer system was attached to both an oral airway and a metal frame fixed to the operating table 10 cm caudad to the chin[1]. Atracurium was administered using a cumulative dose response technique with an infusion to replace drug lost by redistribution and/or metabolism[2]. The percentage reduction in the first twitch height (T_1) was obtained for both muscles and linear regression analysis was performed between the logit transformation of T_1 reduction and the log of the atracurium dose. From these regression lines, the estimated dose to produce 50%, 90% and 95% reduction of T_1 ± SEM (ED50, 90, and 95 respectively) was calculated, and the results were compared by the paired Student's "t" test.

Results. The mean values ± SEM for age and weight were found to be 67.0 ± 21.0 months and 19.5 ± 4.6 Kgs respectively. The sensitivity of the adductor pollicis muscle to atracurium was similar to that of the masseter (Table I). The onset time of maximum effect for the first dose (0.1 mg.kg^{-1}) of atracurium was 189 ± 10.7 s for the adductor pollicis and 147 ± 10.7 s for the masseter which is a significant difference ($p < 0.02$), Student's "t" test). No increases in baseline resting tension were observed for either muscle.

Discussion. This study demonstrated that the masseter muscle had no greater sensitivity to atracurium when compared to the adductor pollicis. In adults, the masseter was found to be 15% more sensitive than the adductor pollicis[1]. Both studies indicate that the masseter and adductor pollicis muscles have similar sensitivities. However, because of interpatient variability, monitoring of the adductor pollicis contraction in response to ulnar nerve stimulation does not necessarily indicate return of adequate upper airway muscle function. The faster onset of neuromuscular blockade for the masseter muscle can be explained by the anatomy of its arterial blood supply and a faster transit time from the left ventricle when compared to the adductor pollicis. The onset of neuromuscular blockade of the diaphragm has been found to precede that of the adductor pollicis and a similar reason has been proposed[3]. These results are comparable to a recent study[4] that reported for the adductor pollicis in children an ED50 and ED95 of 0.135 ± 4.5 and 0.195 ± 10.6 mg.kg^{-1} respectively.

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TABLE I

The Potency of Atracurium at the Masseter and Adductor Pollicis Muscles. ED values in mg.kg^{-1} ± SEM.

	ED50	ED90	ED95
Masseter	0.150 ± 0.013	0.223 ± 0.018	0.254 ± 0.021
Adductor Pollicis	0.145 ± 0.009	0.220 ± 0.012	0.259 ± 0.016

Title: COMPARISON OF RAT CARDIAC ACTOMYOSIN FUNCTION FOLLOWING HALOTHANE AND ISOFLURANE ANESTHESIA.

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Introduction. A time-dependent reversal of the cardiovascular depressant effects of volatile anesthetics during prolonged anesthesia in man has been reported (1,2,3). After approximately 4 hr, heart rate, contractility, and cardiac output returned toward pre-exposure levels. The occurrence of this cardiovascular recovery with various agents is halothane (HAL) > enflurane (ENF) > isoflurane (ISO). A recent study has demonstrated a recovery of contractility in two isolated cardiac muscle preparations, dog heart-lung and guinea pig right ventricle, following prolonged exposure (2 hr) to HAL and ENF (4). Since these latter observations were made in isolated preparations they suggest an intrinsic compensatory increase in cardiac contractility. Our present work evaluates the functional integrity of isolated rat cardiac actomyosin (ACTO) following prolonged anesthetic exposure in vivo.

Methods. Rat (male, Fischer 344) cardiac ACTO was isolated following HAL and ISO anesthesia and evaluated by measurements of intrinsic turbidity, before, and superprecipitation (SPPT), after the addition of ATP. The SPPT reaction is the direct physical interaction of actin and myosin filaments (measured spectrophotometrically, change in absorbance at 560 nm) and is considered an excellent in vitro model of muscle contraction. Dose-response effects of HAL (0.2-1.4% for 0.5 and 4 hr) and cumulative days (1-3) of exposure to 1% HAL (4 hr/day) were studied. Dose-response effects of ISO (1.0-2.0% for 4 hr) were also evaluated. The vapor concentrations were chosen to achieve equal MAC values. The persistence of HAL-induced changes in ACTO were studied in 2-day HAL exposure groups allowed to recover for 4-15 days. Turbidity was determined spectrophotometrically in ACTO suspensions. SPPT parameters included: rate of aggregation (RA), time to peak aggregation (TP), and area under the time-turbidity curve (AUC). Protocols were approved by the Director, Dept. of Animal Care.

Results. HAL anesthesia for 0.5 hr produced no detectable effects on ACTO, but with 4 hr HAL exposure, turbidity of ACTO suspensions increased significantly with dose (p 0.001) and cumulative days of exposure (p 0.001). In comparison, ISO exposure did not affect the turbidity of ACTO. In dose-response studies with HAL, SPPT parameters showed enhanced actin-myosin interaction: RA increased (p 0.05), TP decreased (p 0.001), and AUC decreased (p 0.001). The decrease in AUC was related to the increased intensity and overall shortening of the aggregation reaction (Fig. 1). Alterations in the actin-myosin interaction were much less pronounced with ISO, with only AUC exhibiting a dose-dependent decrease (p 0.05). Covariance analysis (ANCOVA) of the dose-dependent changes in SPPT with HAL and ISO anesthesia demonstrated a significant difference (p 0.05) between the two agents; thus, HAL produced a more rapid actin-myosin interaction (Fig. 2). Following cumulative exposure with HAL, all SPPT parameters were similarly changed as a function of increasing exposure. All HAL-induced changes in ACTO turbidity and SPPT exhibited a time-dependent reversal over a 4-15 day recovery period. The t½'s of recovery ranged from 5 to 10 days, which is consistent with contractile protein turnover in the heart and suggests that reversal is dependent on new protein synthesis.

Discussion. Anesthetic-induced changes in isolated rat cardiac ACTO are more pronounced following HAL than ISO. These observations of an increased intrinsic state of aggregation of cardiac ACTO (turbidity) and intensity of actin-myosin interaction after the addition of ATP (superprecipitation), may help to explain the time-dependent reversal of the negative inotropic effects of HAL, but not ISO, in man and isolated cardiac preparations.

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Fig. 1 Superprecipitation tracings of rat cardiac actomyosin following halothane.

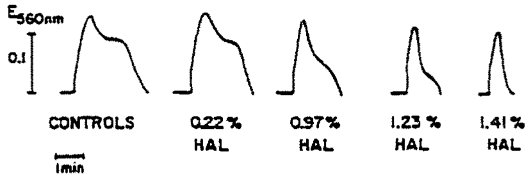
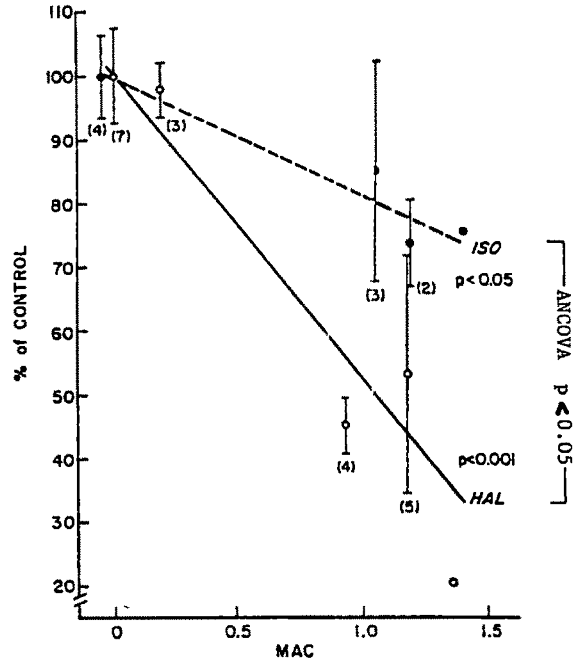


Fig. 2 AUC of superprecipitation tracings vs MAC.



Title: FLUMAZENIL (RO 15-1788) DECREASES THE MINIMUM ALVEOLAR CONCENTRATION OF ISOFLURANE IN DOGS

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Introduction Benzodiazepines are often used clinically to enhance the efficacy of inhalational anesthetics. Intravenous diazepam at a dose of 0.2 mg/kg reduces the minimum alveolar concentration (MAC) of halothane in humans by about 35 % (1). This reduction in MAC is probably due to benzodiazepine facilitation of gamma-aminobutyric acid (GABA) inhibition of synaptic nerve conduction (2). Flumazenil (RO 15-1788), an imidazobenzodiazepine, is a potent, selective benzodiazepine receptor antagonist, with limited agonist activity (3). To better clarify the interaction of the benzodiazepine system and inhalational anesthetics, this study was designed to determine the effect of flumazenil on the anesthetic action of isoflurane in dogs.

Methods The study was approved by the Institutional Committee on Research Involving Animal Subjects. Sixteen mongrel dogs were divided into 3 groups. Group 1 (n=5) received flumazenil at a dose of 0.15 mg/kg; group 2 (n=6) received 0.30 mg/kg and group 3 (n=5) received the drug vehicle 4.5 ml/kg followed by flumazenil 0.45 mg/kg. General anesthesia was induced by mask inhalation of isoflurane and oxygen. Tracheal intubation was accomplished with a cuffed 8.0 mm endotracheal tube without the use of muscle relaxants. Dogs were then mechanically ventilated at a rate of 8 breaths/min at a tidal volume adjusted to produce an end-tidal carbon dioxide tension between 35 and 45 mm Hg. Central venous and femoral arterial catheters were placed and a continuous infusion of lactated Ringer's solution was begun. A heating pad was used to maintain nasal temperature at 37.0 ± 0.5 degrees Celsius. Temperature, EKG and arterial blood pressure were continuously recorded (Siemens 4 channel). Isoflurane concentration was measured by infrared analysis. Exhaled gas was obtained from a 5 1/4 inch 16 gauge teflon catheter inserted through the endotracheal tube.

The (MAC) of isoflurane necessary to prevent purposeful movement in response to tail-clamping was determined according to the method of Eger et al (4). Thereafter, flumazenil, in groups 1 and 2, was injected as an intravenous bolus and MAC was again determined by the same technique. In group 3 MAC was determined after the administration of the drug vehicle and then again after flumazenil. Flumazenil (Hoffman-LaRoche) was given as the aqueous formulation in a 0.1 mg/ml solution. Values for MAC before and after flumazenil and drug vehicle injection were compared by the two-tailed t test for paired data. $p<0.05$ was considered statistically significant.

Results As shown in the table, flumazenil produced a dose-related decrease in isoflurane MAC. The drug vehicle produced no change in the MAC of isoflurane.

Discussion Benzodiazepines produce their effect on the central nervous system by facilitating the interaction of GABA with its recognition site (5). In both behavioral and biochemical studies flumazenil has been shown to antagonize the central nervous system effects of benzodiazepines. Hunkeler et al antagonized the diazepam-induced impairment of mice to climb a wire with orally administered flumazenil (3). In humans, a 2.5 mg i.v. bolus of flumazenil completely reversed the hypnotic effect of a midazolam infusion (6).

There is also evidence that flumazenil has some benzodiazepine agonist activity. Robertson et al showed that i.p. flumazenil reduced seizure activity in rats whose brains were electrically stimulated (7).

Flumazenil may also produce inverse agonist effects (e.g. proconvulsant effects). Corda et al induced seizure activity in rats by administration of subcutaneous isoniazid (8). The subsequent administration of intravenous flumazenil increased the number, duration and severity of convulsant episodes. Inhalational anesthetics, like benzodiazepines, are known to alter central nervous system activities mediated by GABA. Halothane has been shown to prolong the inhibition of mitral cells in the olfactory cortex induced by GABA (9). Furthermore, in rat cerebral cortex slices, halothane has been reported to inhibit the metabolism of GABA (10). Similar effects have been described for chloroform, enflurane and ether (11). Our data indicate that flumazenil potentiates the analgesic effect of isoflurane. In clinical practice flumazenil would be expected to augment the action of isoflurane.

TABLE - MAC of Isoflurane Before and After Flumazenil (Mean ± SD)

n	Flumazenil Dose (mg/kg)	MAC Before (vol %)	MAC After (vol %)	< p
5	0.15	1.39 ± .15	1.23 ± .11	0.05
6	0.30	1.5 ± .35	1.08 ± .20	0.05
5	0.45	1.45 ± .15	1.05 ± .18	0.05
5	vehicle	1.45 ± .15	1.45 ± .15	NS

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Title: AN EDUCATIONAL SIMULATOR FOR THE MANAGEMENT OF MYOCARDIAL ISCHEMIA

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Introduction. In order to properly manage perioperative myocardial ischemia, anesthesiologists must understand the physiology, monitoring techniques, and pharmacologic interventions involved in this complex, life-threatening situation. An educational simulator has been designed that recreates the events surrounding myocardial ischemia in a graphics display on an IBM AT compatible personal computer for use in residency training programs. Residents treat a simulated patient with an ischemic episode by changing the anesthetic, or administering a variety of drugs including beta-blockers, calcium channel blockers, inotropes, vasodilators, vasoconstrictors, and anti-arrhythmic agents. The simulated patient's responses during the ischemic episode are predicted by a mathematical model and displayed on simulated physiological monitors, complete with EKG and pressure waveforms. It is anticipated that practice with a simulator may improve physicians' responses to perioperative myocardial ischemia in patients.

Methods. A cardiovascular model based on experimental evidence was used to predict left ventricular oxygen supply and demand. The left ventricle was represented as a chamber with time-varying elastance, a concept derived from the work of Suga and Sagawa (1). The arterial system was represented by a modified Windkessel with an inductance element for mass of blood in the aorta, aortic compliance, and systemic vascular resistance. This cardiovascular model predicts aortic and left ventricular blood pressure throughout the heart cycle. These pressures vary as a function of preload, contractility, and systemic vascular resistance. Coronary blood flow is assumed to occur only during diastole and is calculated from the integrated difference between aortic and LV pressure divided by an assumed coronary vascular resistance that is increased to mimic a stenosis. Myocardial oxygen supply is predicted from the coronary blood flow, hemoglobin concentration and saturation, and the myocardial extraction ratio for oxygen. Oxygen demand is predicted from the pressure-volume area which is the sum of stroke work and the potential energy expended during contraction, a concept described and validated by Suga (2). The cardiovascular model was combined with pharmacokinetic and pharmacodynamic models for each of the drugs that can be administered. These drugs are listed in the Table. The pharmacokinetic model predicts drug levels in the plasma and an effector compartment based on published pharmacokinetic parameters. The pharmacodynamic model predicts effects of the drugs including changes in heart rate, contractility, systemic vascular resistance, venous compliance, and coronary vascular resistance based on known actions of the drugs.

Results. The simulator is designed to be easy to use. Residents administer drugs to the simulated patient using a mouse rather than a keyboard. The graphics display includes the patient and a physiological monitor which shows the electrocardiogram, arterial blood pressure waveform, pulmonary artery pressure waveform, central venous pressure, pulmonary artery occlusion pressure, and thermodilution cardiac output curves. During the ischemic episode, ST segments change and premature ventricular contractions occur. In addition, contractility decreases and the diastolic stiffness of the left ventricle increases, causing cardiac output to fall and the pulmonary artery occlusion pressure to rise. The resident must manipulate the simulated patient's cardiovascular system using drugs to control the depth of anesthesia, heart rate, contractility, system vascular resistance, filling pressure and arterial blood pressure, to optimize the balance between myocardial oxygen supply and demand. The model also predicts ventricular tachycardia or venticular fibrillation if the myocardial ischemia is not controlled within a few minutes. In these cases, the resident also has to manage the rhythm disturbance including the use of cardioversion.

Discussion. Residents in our training program have enjoyed using the simulator, finding it easy to use and informative. It has stimulated many lively discussions concerning the pathophysiology and treatment of perioperative myocardial ischemia. It is hoped that a series of simulation programs covering a variety of topics will become a useful addition to anesthesiology resident training and may improve anesthesiologists' responses to critical incidents.

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Table. Drug List for the Myocardial Ischemia Simulator

Inhalation Agents
- Enflurane
- Halothane
- Isoflurane
- Nitrous Oxide

IV Anesthetics
- Diazepam
- Etomidate
- Ketamine
- Midazolam
- Thiopental

Narcotics
- Fentanyl
- Morphine
- Sufentanil
- Naloxone

Neuromuscular Agents
- Atracurium
- Metocurine
- Pancuronium
- Succinylcholine
- Vecuronium
- Edrophonium
- Neostigmine

Cardiovascular Agents
- Atropine
- Bretylium
- Calcium Chloride
- Digoxin
- Dobutamine
- Dopamine
- Ephedrine
- Epinephrine
- Glycopyrrolate
- Labetolol
- Lidocaine
- Neosynephrine
- Nifedipine
- Nitroglycerin
- Nitroprusside
- Norepinephrine
- Propranolol
- Sodium Bicarbonate
- Verapamil

TITLE: ABSENCE OF AGONISTIC OR ANTAGONISTIC EFFECTS OF FLUMAZENIL (RO-15,1788) IN ENFLURANE, ISOFLURANE, OR FENTANYL-ENFLURANE ANESTHETIZED DOGS

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Introduction: Flumazenil (RO) is a specific benzodiazepine antagonist,[1] but there is evidence that it has intrinsic pharmacologic activity[2] and that it may hasten recovery from halothane anesthesia.[3] The purposes of this study were 1) to determine the effects of RO on enflurane MAC (EMAC) and isoflurane MAC (IMAC) in the dog, and 2) to examine the effect of RO on the reduction of EMAC by fentanyl.

Methods: Approval for this study was granted by the Animal Investigation Committee of our institution. After the determination of EMAC (Group 1: n=7; Group 2: n=6) or IMAC (Group 3: n=6) by the tail clamp method, a solution of RO in saline (0.35 mg/ml), was administered intravenously 0.5 mg/kg over 1 min. The determination of EMAC (Group 1) or IMAC (Group 3) began 1 min after the end of RO infusion and was completed within 30-45 min. A further 15 min interval elapsed before the next infusion of RO. This sequence was repeated for a series of 3 incremental doses of RO (1.0, 1.5 and 4.5 mg/kg). The highest dose of RO was administered as an infusion over 3 min. After determination of the initial EMAC, a loading dose of FEN followed by FEN infusion (0.8 ug·kg^{-1}·min^{-1}) calculated to reduce EMAC by 60% was administered to the dogs in Group 2; the infusion was maintained at a constant rate throughout the experiment.[4] Following a 60 min observation period, EMAC was determined and 15 min later, RO 1.5 mg/kg was administered. EMAC was then determined for the last time. Arterial blood was taken regularly for blood gas analysis in all 3 groups, and for analysis of FEN concentrations in plasma [FEN] 45 min after initiation of the FEN infusion and every 15 min until EMAC was determined in Group 2. [FEN] was determined by radioimmunoassay. T-tests determined the difference ($p<0.05$) between the degree of EMAC reduction observed and that extrapolated from the [FEN] vs EMAC reduction curve obtained in a previous study.[4] One-way analysis of variance without replication was used to identify differences in MAC reduction associated with subsequent doses of RO.

Results: Regardlesss of the dose administered, RO had no significant effect on EMAC or IMAC (Group 1 and 3), which remained constant throughout the experiment (Table). There was no significant effect of RO on mean arterial blood pressure or heart rate. In Group 2, [FEN] remained stable at 12.5±3.0 (± SD) ng/ml throughout the experiment and reduced EMAC by 60±8% (predicted EMAC reduction = 59±2%).[4] The addition of RO 1.5 mg/kg changed neither the [FEN] (12.2±3.8ng/ml) nor the reduction of EMAC (61±7%).

Discussion: Although flumazenil (RO) has been shown to hasten recovery from halothane anesthesia in mice and humans as determined by changes in motor activity, vigilance and neurology scores[3], small to large doses of flumazenil (RO) did not demonstrate any agonistic or antagonistic interaction with enflurane, isoflurane, or a fentanyl-enflurane combination. The RO doses correspond to those reported to antagonize the effects of midazolam in the dog.[5,6] The absence of any change in EMAC reduction produced by FEN confirms the lack of affinity of RO for opioid receptors.

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Table. EMAC and IMAC before and after incremental doses of RO-15,1788 in dogs.

RO Dose	% Anesthetic in End-Tidal Gas	
mg/kg	EMAC	IMAC
Control	2.32±0.29	1.31±0.08
0.05	2.27±0.32	1.28±0.10
+ 1.0	2.21±0.40	1.30±0.11
+ 1.5	2.24±0.44	1.29±0.11
+ 4.5	2.22±0.46	1.29±0.11

(Values = mean±SD)

Title: **PERIOPERATIVE USE OF TRANSDERMAL CLONIDINE AS AN ADJUNCTIVE AGENT**

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Introduction: Clonidine, the prototypal alpha$_2$ adrenergic agonist decreases anesthetic requirements while providing hemodynamic stability.[1] With the advent of the clonidine transdermal rate-controlled drug delivery system (Catapres-TTS), the supplementation of both anesthesia and postoperative analgesia with clonidine can now be achieved. We report on the use of transdermal clonidine for preoperative sedation, anesthetic supplementation, hemodynamic stability, and postoperative analgesia.

Methods: This study was approved by the Institutional Review Board. Twenty consenting ASA I-II patients scheduled for elective lower abdominal surgery were randomized to receive clonidine high (HI) or low dose (LO) or a placebo in a double-blinded study. The HI group (n=7) was administered 0.2 mg clonidine p.o. and a 10 cm^2 patch of clonidine the night preceding surgery. The LO group (n=8) received 0.2 mg clonidine p.o. and a 7 cm^2 patch. The placebo group (n=5) received an oral and transdermal inert vehicle. Two h prior to surgery, treatment patients received a further oral dose of clonidine (HI=0.4 mg; LO=0.2 mg); additionally all patients received midazolam 0.05 mg/kg i.m. Anesthesia was induced with alfentanil 30 ug/kg, thiopental 2 mg/kg and vecuronium 0.1 mg/kg and maintained with alfentanil 0.5 ug/kg/min, O_2/N_2O 30/70% and vecuronium. Patients received isoflurane to maintain their heart rate and mean arterial pressure within 10% of their pre-clonidine values. At the time of skin closure, alfentanil and vecuronium were discontinued and at the conclusion of surgery the muscle relaxation was reversed and N_2O stopped. Postoperatively patients received morphine by a patient controlled analgesia (PCA) device (Abbott Lifecare). We determined the effect of clonidine on (i) preoperative sedation, (ii) dose of isoflurane required for maintenance of hemodynamic parameters as defined above, (iii) variation of intraoperative heart rate and mean arterial pressure, (iv) time to awakening, (v) plasma alfentanil levels, and (vi) postoperative morphine requirements. Plasma clonidine levels were also measured. Statistical analyses were made using Students t test for unpaired data (significance at $p < 0.05$) and reported as mean ± SD.

Results: There were no significant differences between the three groups with respect to age, sex, weight, ASA status, intraoperative fluid requirements or blood loss. Clonidine treatment groups differed significantly from placebo in preoperative sedation (Fig 1), isoflurane requirements (Fig 2), the coefficent of variation for intraoperative heart rate and blood pressure (Fig 3), time to awakening (Fig 4), mean steady-state alfentanil plasma levels (Fig 5) and PCA morphine requirements (Fig 6). Plasma clonidine levels are depicted in Table 1.

FIG 1.Pre-operative sedation score

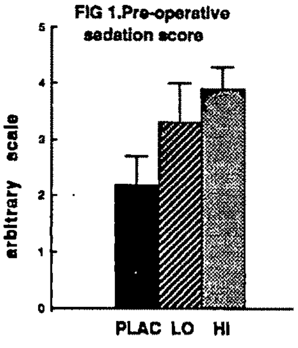

FIG 2. Isoflurane supplementation

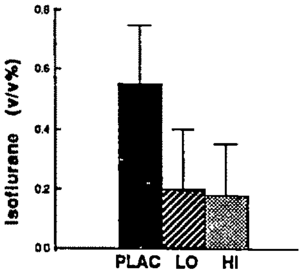

FIG 3. Variation of intra-operative HR and MAP

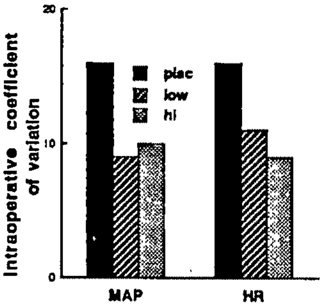

FIG 4. Time to awakening

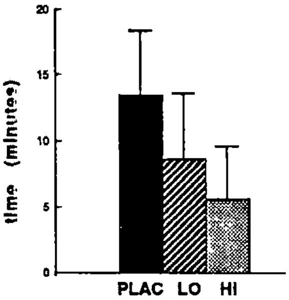

FIG 5. Effect of treatment on plasma alfentanil

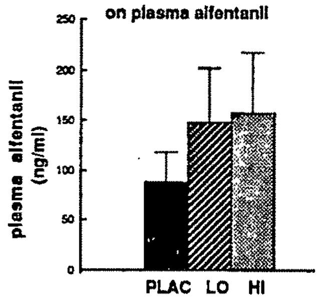

FIG 6. Postoperative analgesic requirements

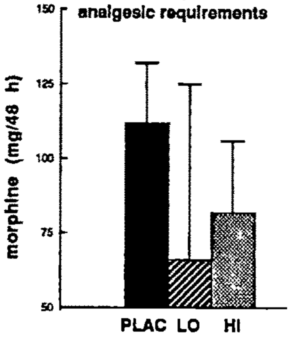

TABLE 1. PLASMA CLONIDINE CONCENTRATIONS, mean +/- SD(ng/ml)

DOSE	PRE-OP	POD#1	POD #2
LO	0.98+/-.25	1.10+/-.41	1.55+/-.72
HI	1.81+/-.75	1.42+/-.53	1.82+/-.33

Discussion: This study extends the utility of clonidine into the postoperative period with the transdermal preparation. In addition to the well-described pharmacodynamic action of alpha$_2$ agonists to potentiate narcotic analgesia,[2] our data suggest a pharmacokinetic mechanism for this action since the plasma alfentanil levels were significantly higher in the clonidine groups (Fig 5). Despite the large intravascular volume shifts and tissue perfusion changes inherent in the surgical patient, the plasma levels achieved with the transdermal preparation were relatively stable. With the lower postoperative PCA morphine requirements in the clonidine-treated groups, an equi-analgesic patient may experience less respiratory depression.

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Acknowledgements: This study was supported by the VA-DOD and the NIH.

TITLE: THE BAIN SYSTEM VS HUMPHREY'S "ADE" SYSTEM: A COMPARISON OF THEIR RELATIVE EFFICIENCIES DURING ASSISTED VENTILATION IN ADULTS

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Introduction: Humphrey's "ADE" anesthesia system is advertised as a universal system for spontaneous, assisted and controlled ventilation.[1] During spontaneous ventilation in the Mapleson "A" mode, the "ADE" has been shown to be more efficient than the Bain system,[2] although requisite fresh gas flows (FGF) for the ADE system have yet to be defined for assisted ventilation. Because assisted ventilation is more commonly used in the clinical setting than spontaneous ventilation, we undertook the present study to compare the relative efficiencies of the Bain and "ADE" systems specifically during assisted ventilation.

Methods: The subjects were 20 healthy adult patients undergoing elective surgery. The protocol was approved by the local IRB and all patients gave informed consent. Anesthesia was induced with a sleep dose of thiopentone and endotracheal intubation was facilitated using 1 mg/kg of suxamethonium. Anesthesia was maintained with 60% N_2O in O_2 and isoflurane using a circle system. After spontaneous respiratory efforts had returned, anesthesia was continued in the following fashion: 10 patients were randomized to the Bain system; the other 10 were randomized to the ADE system in its Mapleson "A" mode (the ADE system does not permit assisted ventilation in the "D" mode). Assisted ventilation was instituted, with spontaneous respiration being permitted during every other breath. Inspired and end-tidal concentrations of CO_2, O_2, N_2O and isoflurane were monitored with a mass spectrometer sampling from the ET tube. VE was measured with a Wright respirometer placed at the ET tube. FGF rate was adjusted to maintain $P_{ET}CO_2$ between 40-45 mm Hg. During intraoperative steady-state anesthesia, cardiovascular and respiratory measurements were performed at 10 min intervals for 30 min. At the end of the study period blood gas tensions were determined. Patients were then returned to the circle system using the same FGF as had been employed during the study period. Data were subjected to statistical comparisons using Student's t-test for non-paired data. $P < 0.05$ was regarded as significant.

Results: Our results are summarized in the Figure. Mean minute ventilation with the Bain and ADE systems were 8.8 L/min ± 0.7 SE and 8.9 L/min ± 0.6 SE, respectively; end-tidal isoflurane concentrations were 1.0% ± 0.09 SE and 0.9% ± 0.07 SE, respectively. An unexpected observation was a lower $P_{ET}CO_2$ with the Bain system despite significantly higher inspired CO_2 tension (20.0 mmHg ± 0.8 SE versus 7.2 mmHg ± 1.8 SE, $P<.05$). Arterial CO_2 tension, however, was not different between the groups. No change in heart rate or BP was observed during the study period with either anesthesia system.

Discussion: The Bain system is known to require a higher FGF rate during spontaneous ventilation than does the ADE system, and this has been advocated as one of the advantages of the ADE system.[1] The present study, however, indicates that assisted ventilation renders the Bain system more efficient than the ADE: that is, maintaining the same arterial CO_2 tension at a significantly lower FGF rate. In adult patients, the Bain system with a FGF rate of 50 mls/kg/min will achieve both satisfactory CO_2 tensions and considerable cost savings as long as ventilation is assisted. This study also points out that the current "Single-lever ADE system" would be improved considerably if it could be reconfigured so that assisted ventilation could be used in the Mapleson "D" mode.

References:

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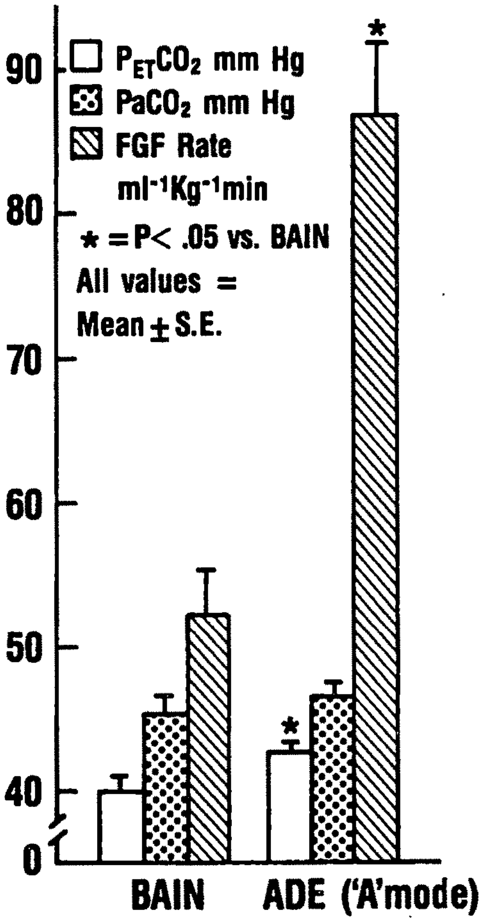

Figure: FGF required to maintain normocapnia using assisted ventilation with either the Bain or "ADE" systems.

TITLE: **HUMPHREY'S "ADE" SYSTEM VS THE MAGILL SYSTEM: RELATIVE EFFICIENCY DURING SPONTANEOUS VENTILATION IN ADULTS.**

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Introduction: Humphrey's ADE anesthesia system is a unique device that functions as a combination of the Mapleson anesthesia systems. It can be converted from the "A" mode to the "D or E" mode by moving a single lever, thus facilitating changeover between spontaneous and controlled ventilation. A fresh gas flow (FGF) rate of 50 ml/kg/min has been recommended to prevent rebreathing with the ADE system,[1] but the FGF required to maintain normocarbia has not been identified. We undertook the present investigation to compare the efficiency of the ADE system in the "A" mode with the classic Mapleson "A" (Magill) system for maintaining normocapnia during spontaneous ventilation in adults.

Methods: The subjects were 20 healthy adult patients undergoing elective surgery. The protocol was approved by the local IRB and all patients gave informed consent. Anesthesia was induced with a sleep dose of thiopentone; endotracheal (ET) intubation was facilitated with 1 mg/kg of suxamethonium. Anesthesia was maintained with 60% N_2O in O_2 and isoflurane. No narcotics were given. Inspired and end-tidal gas concentrations for CO_2, O_2, N_2O and isoflurane were monitored with a Perkin-Elmer mass spectrometer sampling from the ET tube. VE was determined with a Wright Respirometer placed at the ET tube. After surgical incision, patients were allowed to resume spontaneous ventilation, and were randomly assigned either to a Magill system or to an ADE system in its "A" mode. FGF was adjusted to maintain $P_{ET}CO_2$ between 35-45 mm Hg. After 30 minutes of stable anesthesia with one anesthesia system, arterial blood gas tensions and cardio-respiratory parameters were determined and the patient was changed to the other system. FGF was again adjusted to maintain $P_{ET}CO_2$ between 35-45 mm Hg and, at the end of 30 minutes of stable anesthesia, cardiorespiratory data were repeated. The measurements obtained were compared using Student's t-test for paired samples. p<.05 was regarded as significant.

Results: Our results are summarized in the Figure. The FGF rate required to maintain normocarbia with the ADE system was found to be significantly lower than with the Magill system. There was no difference in $PaCO_2$, P_ICO_2 or end-tidal isoflurane concentration ($F_{ET}ISO$) between the two systems (Table 1), and no change in heart rate or BP was observed during the study.

TABLE 1

PARAMETER	ADE	MAGILL
PaCO2 (mmHg)	46.50 ± 0.80	45.80 ± 0.90
PICO2 (mmHg)	5.26 ± 0.61	5.16 ± 0.61
FETISO (%)	0.88 ± 0.06	0.88 ± 0.07
All values = Mean ± SE.		

Discussion: In this carefully controlled randomized study we found that the ADE system is more efficient than the Magill system. Although the FGF rate required with ADE system is higher than recommended[1], it was still significantly lower than that required by the Magill system. As long as end-tidal CO_2 tension is monitored for patient safety, the ADE system not only offers savings in FGF during spontaneous ventilation, but also has the advantage of being able to convert easily from the Mapleson "A" mode to the Mapleson "D" mode for controlled ventilation. We conclude that the Magill system is not as efficient as the ADE system for conserving expensive anesthetic gases during spontaneous ventilation.

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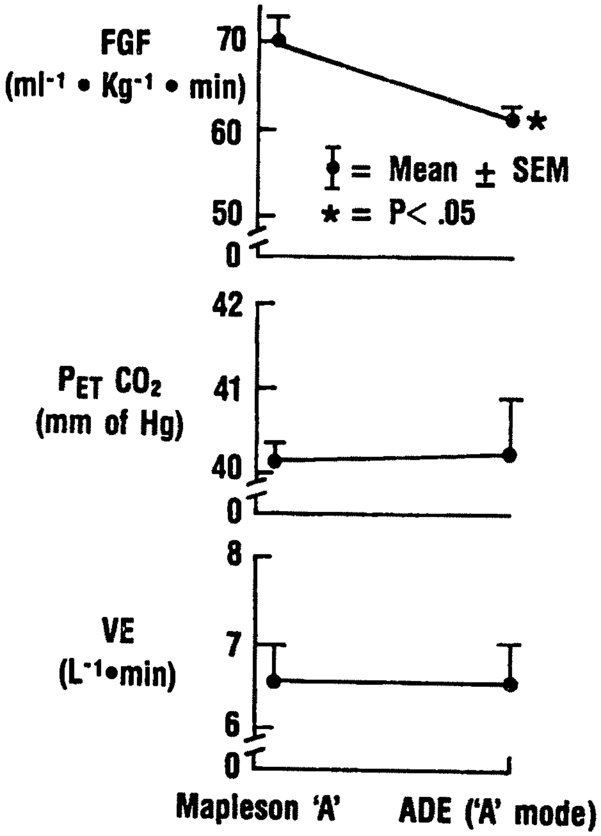

Figure: Changes in required Fresh Gas Flow (FGF), end-tidal CO_2 tension ($P_{ET}CO_2$) and minute ventilation (VE) for the Mapleson A and "ADE" systems during spontaneous ventilation.

Title: A QUANTAL ANALYSIS OF THE DOSE-RESPONSE FOR TRACHEAL INTUBATION USING MIVACURIUM AS THE TEST RELAXANT.

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Introduction

Numerous studies evaluating the clinical maneuver of tracheal intubation have been published. Nearly all are defective in one or all of the following areas: (1) the studies are poorly controlled with respect to baseline anesthetic conditions; (2) the timing of intubation is not standardized; (3) most importantly, the concept of dose-response is totally ignored. In the following study, tracheal intubation is treated as a pharmacological end-point and analyzed in quantal fashion: that is, the effect of increasing dosage of mivacurium[1,2], the test relaxant, on the incidence of good-excellent conditions for tracheal intubation two minutes after mivacurium administration is examined under standardized anesthetic conditions. The generation of a dose-response curve then permits various quantitative comparisons with other relaxants in a manner not previously possible.

Methods

ASA Class I-II patients (n=36) with normal airway anatomy, ages 18-59, weighing 45-110 kg, undergoing elective surgery, gave IRB-approved written informed consent. Patients received morphine (0.1-0.15 mg/kg) and diazepam (0.1-0.2 mg/kg) preoperative medication. Baseline measurements (BP by oscillotomometer, EKG, HR, adductor pollicis twitch at 0.15 Hz) were obtained for 5 minutes during preoxygenation in the operating room. Four groups (n=9 or 18) were evaluated. At time zero each patient received a sedating dose of fentanyl (1.5-3 mcg/kg) followed 2.5 minutes later by thiopental (5 mg/kg). 30 seconds later the intubating dose of relaxant was administered. Ventilation with oxygen was controlled by mask until intubation two minutes after relaxant administration.

Intubation was scored according to Table 1. Dose-response curves for intubating conditions 2 min after relaxant injection, during fentanyl/thiopental induction of anesthesia were generated. In each group, incidence of individuals responding with good/excellent conditions for intubation was converted to a percentage and plotted on log-probit scales. The dose-response curve was treated thereby as an all or none response according to the method of Litchfield and Wilcoxon[3]. That is, did each individual patient respond to the treatment with good/excellent conditions for intubation or not? Statistical analysis was by ANOVA, p<0.05 considered significant.

Table 1

Classification of Intubating Conditions

Grade	Description
Excellent	No response to intubation
Good	Slight coughing on intubation
Poor	Jaw not relaxed, cords moving, intubation accompanied by bucking, coughing, movement
Impossible	Jaw tightly shut, cords adducted

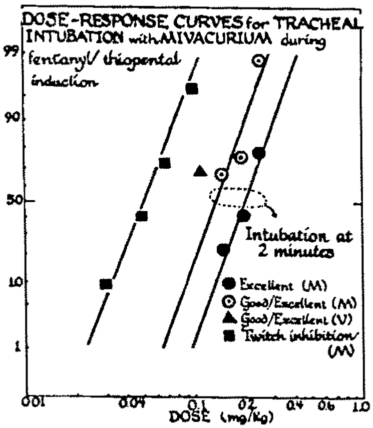
Table 2

Group	Relaxant	Dose mg/kg)	ED95 Multiple	Graded Excel.	Graded Good/Excel.
A	Mivacurium	0.15	2	22%	67%
B	Mivacurium	0.20	2.5	41%	76%
C	Mivacurium	0.25	3	78%	100%
D	Vecuronium	0.11	2	44%	67%

Results

Data are listed as group means, SE's omitted for space (Table 2). The trachea was successfully intubated according to protocol at two minutes after relaxant in all subjects except two given mivacurium 0.15 mg/kg where additional time for onset of block and/or additional mivacurium and thiopental was required. Patients receiving vecuronium 0.11 mg/kg had intubation scores not significantly different from those receiving mivacurium 0.2 mg/kg. Recovery to 95% twitch height among patients given mivacurium was significantly faster than with vecuronium (28 min vs 69 min). An ED_{50} for excellent intubating conditions at 120 seconds with non-primed doses of mivacurium was calculated at 0.20 mg/kg (95% C.L. = 0.17-0.23). An ED_{50} for good/excellent intubating conditions was calculated at 0.13 mg/kg (95% C.L. = 0.10-0.17). An ED_{90} for good/excellent intubating conditions was plotted at 0.2 mg/kg and an ED_{95} at 0.23 mg/kg.

Figure 1



Discussion and Conclusion

The curves in Fig. 1 show that excellent intubating conditions are achieved at dosage which is 50% higher than dosage required for good/excellent conditions, i.e., the curve shifts to the right by a factor of about 1.5. This dosage increase, however, may increase side effects in the case of mivacurium or increase duration of effect in the case of vecuronium. An ED95 of 0.25 mg/kg mivacurium for good/excellent intubating conditions two minutes after relaxant administration represents 3 X the ED95 for twitch inhibition.[4] (Fig. 1). The two dose-response curves do not deviate significantly from parallelism so that the two neuromuscular responses (twitch inhibition and tracheal intubation) seem separated by a dosage factor of about three. Additional comparisons based on parallelism of dose-response curves suggest (1) that vecuronium's ED95 for good/excellent conditions for tracheal intubation under the same protocol is 0.16 mg/kg, also 3 X ED95; and (2) that "priming" e.g., in the case of mivacurium generates a dose-response curve for intubation at 90 sec after relaxant administration which is not significantly different from that presented herein at 2 min after single-bolus dosing without priming. In other words, the dose-response curve shifts to the left by a time-factor of 30 seconds.

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Title: PHARMACOKINETICS OF INTRATHECAL BUPIVACAINE AND MORPHINE WITH AND WITHOUT EPINEPHRINE FOR CESAREAN SECTION

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Introduction. Spinal anesthesia (SA) with bupivacaine (B) is becoming increasingly popular for cesarean section. Morphine (M) can also be administered intrathecally at the time of SA induction to provide post-operative analgesia. However, little information is available on the plasma pharmacokinetics and urinary elimination of B and M after spinal administration in obstetrical patients. Also lacking is sufficient data on the effect of epinephrine on the disposition of these drugs. This study reports plasma and urinary levels of free and conjugated M, and plasma B levels in postpartum patients.

Methods. The protocol was approved by the Review Board and patients (n=14) gave informed consent. Patients presenting for cesarean sections were randomly assigned to two equal groups. Following prehydration with 1500 ml Ringer's lactate SA was induced to a T4 level. Patients in group 1 received hyperbaric B 12 mg as 0.75% solution with 8.25% dextrose plus 0.6mg M. Patients in group 2 received the same amounts of B and M but also received 50 μg of epinephrine. Venous blood (EDTA anticoagulant) and urine samples were collected prior to the spinal anesthetic and at .25, .5, 1, 2, 3, 6, 12 and 24 hours. Free morphine concentration was assayed using a specific radioimmunoassay (0.3% cross-reactivity with morphine-3-glucuronide, Coat-A-Count, Diagnostics Product Corp, Los Angeles, Calif). The concentrations of conjugated morphine in plasma and urine samples were measured following incubation with glusulase (Endo Labs, Garden City, N.Y.; 4000 uβ-glucuronidase + 700 u sulfatase). Urinary excretion was calculated by multiplying concentration by volume collected for each time interval. B was measured in plasma samples by gas chromatography. Area under the curve (AUC), volume of distribution (VDss), the terminal half-life (t1/2β) and plasma clearance (Cl) were calculated (1). Cord blood obtained at delivery (UA and UV) was assayed for M and B. Results were analyzed using the t-test.

Results. B levels peaked in the plasma at 0.5 hours in both groups with peak levels numerically higher in group 1 (Fig. 1). The difference was not statistically significant. The AUC, Vdss, t1/2β, and Cl for B were not statistically different between the groups (Table). Free plasma M concentrations were at or below the lower limit of assay sensitivity (0.6 ng/ml) and therefore could not be subjected to pharmacokinetic analysis. Multiple peaks were seen with plasma conjugated M with evidence of conjugation noticeable as early as 15 minutes after spinal administration. Because of the multiple peaks no accurate pharmacokinetic analysis could be performed. In both groups urinary free and conjugated M excretion peaked at 6 hours, with more conjugated M being excreted than free M (Fig 2). The difference between the groups was not significant. M and B were levels were not detectable in umbilical cord blood.

Discussion. Burn et al (2) have recently reported that addition of epinephrine to B did not significantly decrease plasma B concentrations after intrathecal administration in non-obstetrical patients. Our data show that addition of epinephrine does not alter disposition of intrathecally administered B or M. Our data further show that M is absorbed rapidly from the intrathecal space following which it is conjugated and excreted in the urine. In summary, epinephrine does not affect the systemic absorption of M or B from the subarachnoid space in obstetrical patients.

References.

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Table. Plasma Bupivacaine Pharmacokinetics

	BUPIV	BUPIV + EPI
AUC	295 (87)	403 (105)
VDss	248 (29)	167 (35)
T1/2	4.42 (1.15)	3.22 (1.39)
Cl	1692 (733)	994 (880)

Legend: AUC=area under curve; VDss=volume of distribution in liters; T1/2β =β half life in min; Cl =clearance in ml/min. Data are mean +/- 1SE (figures within parentheses).

Fig 1. PLASMA BUPIVACAINE (ng/ml)

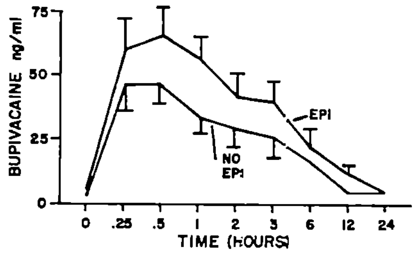
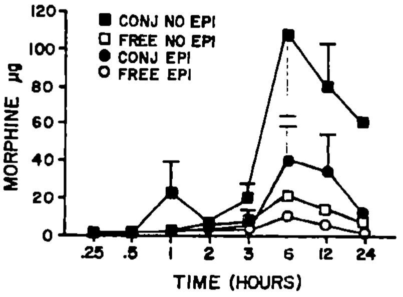


Fig 2. URINARY MORPHINE EXCRETION (μg)



Title: **HEMODYNAMIC RESPONSE TO LOW DOSE EPINEPHRINE INFUSIONS UNDER HYPOTENSIVE EPIDURAL ANESTHESIA FOR TOTAL HIP REPLACEMENT**

Authors: NE SHARROCK, M.B.ChB., R. MINEO, M.S., C.R.N.A.

Affiliation: Department of Anesthesiology, Hospital for Special Surgery, New York, NY

Introduction: Epidural anesthesia reduces the frequency of deep vein thrombosis(DVT) following total hip replacement(THR) by 50% to 25% as compared to general anesthesia1. This reduction has been attributed to increased blood flow in the lower extremities2. Epidural anesthesia and controlled hypotensive anesthesia are associated with reduced operative blood loss during total hip arthroplasty3. To minimize the risks of DVT and intraoperative bleeding, a technique to reduce blood pressure, yet maintain cardiac output under epidural anesthesia, has been developed.

Methods: Following Institutional Review Board approval, consents were obtained from patients requiring invasive hemodynamic monitoring during THR to investigate the hemodynamic effects of hypotensive epidural anesthesia. Indications for pulmonary artery catheters included revision or bilateral THR, or significant cardiopulmonary disease. Patients with low baseline cardiac indexes(CI), or beta blockade were excluded from the study. All patients had pulmonary artery catheters and radial artery lines inserted percutaneously under local anesthesia using minimal intravenous sedation(midazolam 1-3mg and fentanyl 25-50mcg). Patients received 50cc/hour D51/2NS from the night before surgery and were not fluid loaded before or after the epidural injection. Cardiac outputs were measured in triplicate using thermodilution technique. Hemodynamic data was recorded in the lateral position with the operative side up before the epidural anesthetic(baseline). Epidural anesthesia was performed at the L2-3 interspace with 15 to 25 ml of 0.75% plain bupivacaine via a 17 gauge Tuohy needle to achieve an anesthesia level to T4 or above. In 52 patients central venous epinephrine infusions of up to 5mcg/min were instituted immediately following the epidural injection and the rate adjusted to maintain a mean arterial pressure(MAP) of 50mmHg or 50% of the initial pressure(which ever was higher). When MAP had been kept at 50mmHg for ten minutes with a steady epinehrine infusion rate(stabilized), hemodynamics were again recorded. In addition 20 patients were likewise studied without epinephrine infusions. Patients were classified to infusion rates of zero, <1, 1-2, and >2 mcg/min of epinephrine required to achieve a stable 50 mmHg MAP. Changes in hemodynamic parameters from baseline to stabilized were analyzed(ANOVA) for differences between groups to demonstrate a dose response to the low dose epinephrine infusion.

Results: There were no significant differences in the age, height, weight, sex, or baseline hemodynamic parameters among the patient groups. Means and standard deviations of the hemodynamic variables at different epinephrine infusion rates are shown in table 1. Without an epinephrine infusion there was a statistically significant(p<o.01) fall in MAP, CI, stroke volume(SV), heart rate(HR), pulmonary artery diastolic(PAD) pressure, and left ventricular stroke work index(LSWI) following epidural anesthesia. Epinephrine infusions, by progressively increasing stroke volume, allowed CI to be maintained at baseline values when rates of greater than 2 mcg/min were utilized Figure 1. HR, PAD, and LSWI, did not change significantly(p>0.1) with increasing infusion rates. Systemic vascular resistance(SVR) fell progressively as infusion rates increased.

Discussion: Blockade of cardiac sympathetics may contribute significantly to circulatory collapse following extensive epidural anesthesia. Low dose epinephrine infusions of 2-5 mcg/min allowed sufficient control of reductions in MAP for deliberate hypotension during total hip replacement yet reversed cardiac depression.

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	NO EPINEPHRINE		<I UG. EPINEPHRINE	
	N = 26		N = 6	
	BASELINE	UNTREATED	BASELINE	TREATED
CI	3.1 ±.766	2.0 ±.398 x	3.0±.443	2.5±.415
MAP	98.3±14.1	53.8±6.1 x	93.8±6.6	56.3±4.8
PAD	9.1±3.1	5.7±2.4 x	9.3±4.3	7.0±3.5
HR	72.3±13.4	64.4±11.5 x	68±11.3	66.6±6.5
SV	81.0±22.6*	56.8±14.7 x	77.6±12.6	65.8±12.9
LSWI	52.7±14.6	20.0±6.6 x	51.5±7.0	25.3±5.9
SVR	1408.3±460	1194.2±302.2	1390.1±345.1	991± 193.1

	1-2 UG.EPINEPHRINE		2-5 UG EPINEPHRINE	
	N= 26		N = 20	
	BASELINE	TREATED	BASELINE	TREATED
CI	3.4±..653	2.9±.765	3.2±.571	3.1±.54*
MAP	102.6±14.1	54.0±6.1	105.5±20.9	48.6±3.9*
PAD	11.2±5.1	8.2±3.7	9.9±4.0	7.2±3.1
HR	80.3±13.7	71.3±13.2	75.9±12.3	67.6±11.7
SV	77.3±21.0	75.4±23.9	78.7±22.8	84.6±20.6*.
LSWI	54±13.0	26.2±8.5	59.3±15.2	27.7±6.8
SVR	1359±345.1	850.2±311.7	1477.7±494	690.8±221.9*
	X P < 0.01 T TEST			
	* P < 0.05 ANOVA			
		TABLE 1		

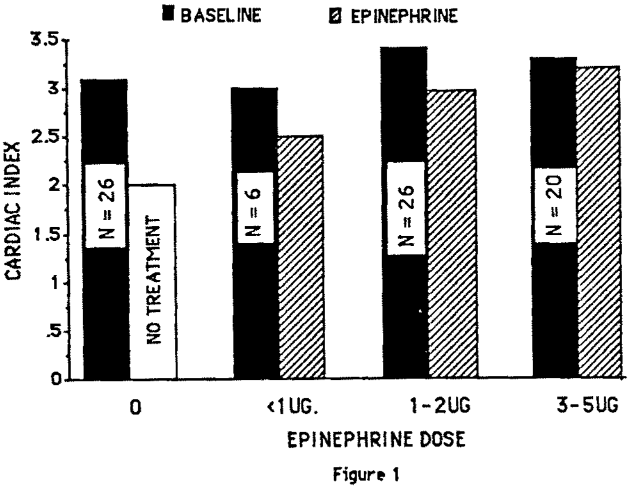

Figure 1

Title: **IS HYPOTENSIVE ANESTHESIA SAFE IN TREATED HYPERTENSIVE PATIENTS? EXPERIENCE WITH EPIDURAL ANESTHESIA**

Authors: **NE Sharrock, M.B., Ch.B., R Mineo, M.S., C.R.N.A., B. Urquhart, R.N.**

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Introduction: In total hip replacement bleeding is a major cause of morbidity and transfusion carries risks. Hypotensive anesthesia has the benefit of reducing blood loss in total hip replacement(THR) and thereby may reduce the potential danger of transmitting blood born infections. The use of hypotensive anesthesia for hypertensive patients is controversial due to concerns over the adequacy of intracranial and myocardial blood flow. Autoregulation of brain blood flow is impaired in hypertensive patients as the blood pressure falls[1], but animal data suggests that this may be normalized in treated hypertensive rats[2]. Also, regional coronary blood flow may fall disproportonately to the needs of a hypertrophic ventricle leading to cardiac ischemia and ventricular dysfunction. It would be helpful to establish the safety of this technique in hypertensive patients.

Method: Following Instituional Review Board approval, consents for study were obtained from 69 THR patients. Thirty-one were diagnosed, controlled, treated hypertensives. Treatment including ß-blockers, diruetics, calcium channel blockers, and A.C.E. inhibitors. Patients were followed up for evidence of cerebral dysfunction by assessing the rates of stroke or confusion in the post operative period. All patients had pulmonary, and radial arterial catheters inserted under local anesthesia. Between 15 and 25 ml of plain 0.75% bupivacaine was injected through a 17 gauge epidural needle at the L2-3 interspace to achieve a sensory anesthetic level of T4 or above. In the lateral decubitus position, triplicate thermodilution cardiac outputs were measured prior to epidural anesthesia and intermittently during the case. Patients were minimally sedated with a combination of midazolam and fentanyl intraoperatively and received 3 L/min nasal O_2 throughout the case. Following the epidural anesthetic mean arterial pressure (MAP) was allowed to fall to approximately 50 mm/Hg. and was maintained at this level throughout the case. The patients sensorium was reassessed constantly during the induction of hypotension and regularly throughout the case by engaging the patient in coherent conversation. Cardiac index (CI) and MAP were maintained with a central venous infusion of epinephrine 1 - 5 mcg/min.

Results: There was no significant difference in age, height, and weight between groups (Table 1). All patients in both groups remained fully lucid and communicative during the induction and maintenance of hypotension. Patients showed no evidence or somnolence, confusion, or local neurological deficits intraoperatively. There were no postoperative strokes reported. Only one hypertensive patient became confused postoperatively compared to two in the non-hypertensive group. The hemodynamic response to the induction and maintanence of epidural hypotensive anesthesia with low dose epinephrine infusions was no different between hypertensive and nonhypertensive patients (Table 2).

Discussion: Epidural anesthesia in awake minimally sedated patients enables a direct and constant assesment of neurological status. This provides a clinical setting where hypotensive anesthesia in hypertensive patients can be examined. This data suggests that treated controlled hypertensives respond in a similar manner to nonhypertensives with the induction of epidural hypotension . The ultimate advisability of this technique awaits more extensive clinical trials.

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HYPERTENSIVE n = 31

SEX	MALES 14	FEMALES 17
AGE	68.3 ± 9.3	73.8 ± 8.7
HGT	169.6 ± 8.6	153.4 ± 9.6
WGT	78.5 ±11.2	66.3 ±13.8

NORMOTENSIVE n = 38

SEX	MALES 13	FEMALES 14
AGE	65.4 ± 13.7	74.4 ±10.4
HGT	169.3 ± 8.1	156.2 ± 7.7
WGT	86.4 ± 11.7	62.5 ± 8.8

TABLE 1

HYPERTENSIVE n=31

	Baseline	Stablized
CI	3.1 ± .56	2.7 ± 0.68
MAP	106.8 ± 18.8	55.7 ± 8.3
PAD	11.6 ± 4.6	8.3 ± 3.3
HR	78.1 ± 13.0	68.2 ± 13.2
SV	72.2 ± 19.3	73.4 ± 23.5
LSWI	53.3 ± 12.2	26.9 ± 9.2
SVR	1527. ± 485.	928. ± 292.

NORMOTENSIVE n=38

	Baseline	Epidural
CI	3.2 ± 0.75	3.0 ± 0.67
MAP	100.1 ± 15.0	52.5 ± 6.7
PAD	10.5 ± 4.6	7.9 ± 3.4
HR	74.4 ± 13.5	66.5 ± 12.1
SV	80.2 ± 21.5	84.1 ± 22.4
LSWI	55.6 ± 15.3	28.5 ± 6.7
SVR	1380. ± 410.	799. ± 375.

All $p > 0.1$ hyper- vs normotensives

TABLE 2

Title: **THE VALUE OF AUTOLOGOUS BLOOD DONATION AND HYPOTENSIVE ANESTHESIA IN REDUCING HOMOLOGOUS BLOOD REQUIREMENTS FOR TOTAL HIP REPLACEMENT(THR)**

Authors: **NE Sharrock, M.B., Ch.B., R Mineo, M.S., C.R.N.A., G Go, B.S.**

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Introduction: Preoperative banking of patients own blood for purposes of retransfusion perioperatively may have a role in minimizing homologous blood transfusion. Also, hypotensive anesthesia has been found to reduce blood loss in total hip replacement but effect on transfusion requirements is less clear. Many argue that due to inadequate intraoperative hemostasis the patients hypotensed during their surgery will bleed more postoperatively and so negate any benefit from reduced intraoperative blood loss. A clearer understanding of the value of each would be helpful due to the risks of blood born infections.

Methods: A retrospective review of 679 consecutive THRs done by five different surgeons from January 1986 to April 1987 was undertaken. Patients age, weight, type of procedure (unilateral or revision), surgeon and anesthesiologist was recorded from patient charts, preoperative and discharge hemoglobin records from hematology department, units of homologous or autologous blood transfused from blood bank records, and anesthetic type from anesthetic records. Estimated blood loss was routinely calculated by measurement of suctioning and weighing of sponges. Anesthetics were classified as hypotensive if mean arterial pressure was <60 mmHg throughout the operation as measured by arterial line. Normotension was defined as blood pressure consistently above 90 sytstolic. Patients received either spinal, general, or epidural anesthesia. The mean number of homologous units transfused between groups was compared by two way analysis of variance (MANOVA).

Results: There were no statistically significant differences in patients age, sex and weight between the hypotensive and normotensive groups. There was no significant difference in preoperative and discharge hemoglobins between the groups. Reductions in the mean number of units of homologous blood transfused for hypotensed and normotensed patients with availability of autologous blood in patients having unilateral or revision THRs are shown in Figure 1. There was a similar reduction in measured intaoperative blood loss for both unilateral and revision THRs (Table 1 & 2).

Discussion: Homologous blood unit transfusions were reduced by autologous banking in unilateral and revision THRs. The autologous program is effective in reducing the incidence of transfusion in unilateral THR under both normotensive and hypotensive anesthesia, and in revision procedures if hypotensive anesthesia is used. Hypotensive anesthesia is effective in reducing homologous transfusion requirements for unilateral THR only if the patient has not banked autologous blood and revision THR regardless. Autologous blood banking and hypotensive anesthesia has resulted in a cumulative reduction in the number of homologous blood units transfused.

The reduction in intaoperative blood loss produced by hypotensive anesthesia is manifested by an overall reduction in transfusion requirements, suggesting that patients having hypotensive anesthesia do not bleed more postoperatively.

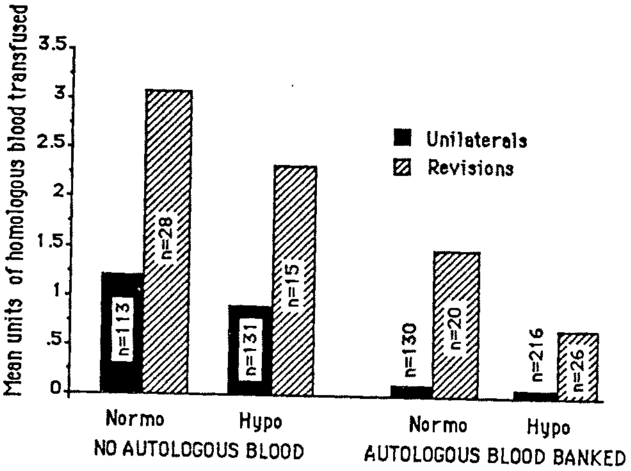

Figure 1

UNILATERAL THR

	NORMOTENSIVE (n=243)	HYPOTENSIVE (n=347)	
Units Homologous Blood Transfused	0.626±1.01	0.395±1.00	p=.0063
Pre-op Hgb	13.46±1.42	13.71±1.43	
Discharge Hgb	10.85±1.18	11.19±1.26	
Difference Hgb	2.61	2.52	p=.4387
EBL	442±279	303±192	p=.0001

Table 1

REVISION THR

	NORMOTENSIVE (n=48)	HYPOTENSIVE (n=41)	
Units Homologous Blood Transfused	2.417±2.90	1.293±1.78	p=.034
Pre-op Hgb	13.25±1.69	13.31±1.33	
Discharge Hgb	10.36±1.12	10.68±1.31	
Difference Hgb	2.65	2.63	p=.4215
EBL	1093±801	653±518	p=.0037

Table 2

Title: HOW STRESSFUL IS THE CESAREAN SECTION TO THE FATHER?

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Introduction. It is routine practice for fathers to be present in the delivery room at their baby's birth. Their presence lends support and encouragement to the mothers during labor. The fathers also benefit because this gives them the opportunity to share in the joy of the birth as well as the chance to develop early bonding with the infant(1,2). Having fathers present during cesarean delivery is also common practice so that they may support mothers during an even more stressful situation with anesthesia and surgery(3,4). It has, however, been observed that some fathers developed symptoms such as sweating, nausea,lightheadedness, and fainting on these occasions. This is believed to be related to the cardiovascular responses to being involved in a stressful situation

The purpose of this study was twofold:(1) to determine the stress level of fathers who are present in the operating suite during the cesarean delivery of their baby and (2) to identify potential risk factors for these fathers.

Methods. Participants for this study were selected from a group of fathers who volunteered to be in attendance at the elective cesarean delivery of their baby. Following institutional approval informed consent was obtained from each study participant. A medical history was obtained and an ASA classfication was determined and recorded for each father. Arterial blood pressure and heart rate were measured by an automated device (Space Lab) twice at five minute intervals. An electrocardiographic tracing, using a modified CS5 lead, was obtained. When adequate epidural anesthesia was achieved in the mother, the father was brought into the operating room and seated in a chair beside the mother. Arterial blood pressure and heart rate were remeasured prior to delivery, during delivery and again 5 minutes following the delivery of the infant. During this study period, a continuous electrocardiographic recording was obtained and analyzed for arrhythmias and ST segment depression. The results of the arterial pressure and heart rate were tabulated and statistically analyzed.

Results. Seventy-six fathers participated in this study. Of these, 15 were classified as ASA Class 2. The mean age was 33 years. The arterial blood pressure on admission was 128±13/75±9 mmHg. (mean ± S.D.) The heart rate was 77±9 beats/min. The BP rose to 144±24/88±9 mmHg at delivery and returned to 133±17/79±14 mmHg 5 minutes after delivery, and the heart rate changed to 98±20 beats/min at delivery and 79±14 beats/min in 5 minutes. At delivery, the arterial blood pressure was measured above 140/90 mmHg in 31 fathers (40%) and above 160/110 mmHg in 4 fathers. A heart rate was recorded above 120 beats/min. in 5 fathers and above 140 beats/min. was noted in 6 fathers. Premature ventricular contractions were also noted in 3 fathers. One father demonstsrated ST-segment depression. Severe bradycardia (Heart rate<40 beats/min) was noted in 2 fathers with one father fainting. The fathers expecting a child for the first time showed significantly higher blood pressure and heart rate changes than the fathers who had had at least one child.(Table)

Discussion. A significant number of fathers who participated in elective cesarean childbirth showed transient elevation of arterial blood pressure and heart rate during the delivery. Although the changes in hemodynamics were transient, a few fathers demonstrated hypertension(BP>160/110), severe tachycardia(>140bpm), premature ventricular contractions and/or severe bradycardia, indicating that attendance in cesarean delivery can be emotionally stressful for some fathers. Therefore, we recommend that fathers who wish to be present at cesarean delivery should be informed of the potential risks of hemodynamic stress, particularly fainting.

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Table

	Blood Pressure(mmHg)		Heart Rate(Beats/min)	
	First Time Father (N=33)	Non-first Father (N=43)	First Time Father (N=33)	Non-first Father (N=43)
Prior To Delivery	127±13/76±9	130±16/78±13	83±14	79±14
During Delivery	151±20/89±11	139±29/86±7	105±19	94±21
5 Minutes Following Delivery:	136±16/84±12	128±24/78±10	85±14	79±14

All values are mean ± S.D.. Systolic blood pressure and heart rate values during delivery are statistically different between first time fathers and non-first time fathers($p<0.05$).

Title: EXPIRATORY MUSCLE ACTIVITY DURING HALOTHANE ANESTHESIA IN CHILDREN

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Introduction: Activity of the abdominal muscles during expiration has been demonstrated in most anesthetized adults studied with electromyography (EMG).[1,2] If present in children, abdominal muscle activity would preclude the use of non-invasive tests of respiratory mechanics such as the passive flow-volume ($\dot{V}$-V) technique, since the expiratory time constant (τa) would be decreased during active expiration. Therefore we studied abdominal muscle activity using EMG during induction of anesthesia in healthy children and its effect on τa.

Methods: With approval from the institution's Human Experimentation Committee, informed consent was obtained from the parents of 8 children, 6 months to 7 years of age scheduled for elective surgery. All children were ASA physical status I. The children were studied after induction of anesthesia with increasing concentrations of halothane in a 2:1 mixture of N_2O and oxygen via a Jackson-Rees modified Ayre's t-piece with a tight fitting facemask. End-tidal halothane concentration (Feh) was measured continuously at the mask. Abdominal wall EMG and the expiratory time constant (τa) were measured during induction of anesthesia. In 6 children measurements were continued during controlled ventilation with oxygen after neuromuscular paralysis with succinylcholine, 2 mg/kg body weight, but before endotracheal intubation. After intubation, surgery commenced.

Mask pressure was measured from a side port on the mask and the signal was analyzed and displayed on a computer. A pneumotachograph was connected to the mask for measurement of flow ($\dot{V}$) and this was integrated to produce volume (V). During quiet breathing at end-inspiration, the distal port of the pneumotachograph was briefly occluded until the mask pressure signal reached a plateau. The occlusion was then released and the subsequent expiration was analyzed by computer in a $\dot{V}$-V format. The inverse of the slope of the $\dot{V}$-V curve of the post-occlusion expiration is the expiratory time constant during spontaneous breathing (τa). At least 8 such $\dot{V}$-V maneuvers were performed. Following paralysis, the expiratory time constant of paralyzed expiration (τp) was measured during controlled ventilation and was used as the baseline to which τa was compared.

Abdominal wall EMG was recorded from two electrodes placed at the lateral border of the rectus abdominus 1-2 cm caudad to the costal margin. The EMG signal was amplified and displayed on an oscilloscope as well as recorded on magnetic tape. The EMG during paralysis was used as the baseline EMG to which the signals recorded during spontaneous breathing were compared. In addition, the signal was electronically processed to produce a moving time average (MTA).[3] The flow signal from the pneumotachograph and the EMG and MTA were recorded simultaneously to facilitate comparison of the abdominal wall activity and the phase of breathing.

Results: One subject showed no EMG activity throughout induction. Seven subjects showed phasic abdominal muscle EMG activity during expiration (Figure). In 3 subjects the activity disappeared with increasing depth of anesthesia. In 3 other subjects activity decreased, but did not disappear with increasing depth and in one subject marked phasic EMG activity persisted throughout induction. However, the decrease in activity did not always occur at the same Feh. In the 4 subjects in whom EMG activity was absent during deep anesthesia, mean τa was 10% greater than mean τp. In 2 subjects in whom EMG activity decreased but did not disappear during induction, τa was 65% (Figure) and 88% less than τp, suggesting that τa was decreased by the persisting expiratory muscle activity in these 2 subjects.

Discussion: We detected phasic activity of the abdominal muscles in 7 out of 8 children during induction of anesthesia with halothane. Although the phasic activity decreased or disappeared during deep anesthesia in all but 1 subject, the presence or absence of activity could not be predicted by the shape of the $\dot{V}$-V curves or by Feh. The comparison of τa with τp was the only useful indicator of expiratory muscle activity. Since expiratory muscle activity invalidates the passive $\dot{V}$-V technique, and since EMG testing is usually impractical, we propose that τa be compared to τp in all subjects who undergo non-invasive tests of respiratory mechanics. Passive conditions necessary for the technique can only be assumed when τa is equal to τp.

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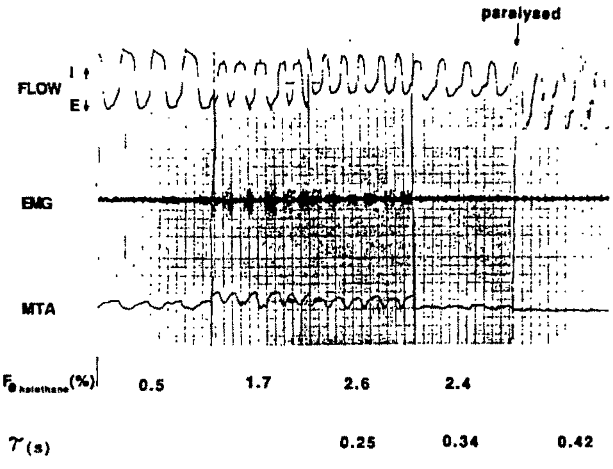

Flow, EMG and MTA signals from one patient showing phasic expiratory muscle activity during induction of anesthesia with halothane.

Title: HEMODYNAMIC AND PHARMACOKINETIC PROFILES OF THREE INFUSIONS OF HIGH-DOSE SUFENTANIL ANESTHESIA

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Introduction: Cardiovascular effects of high-dose sufentanil (S) anesthesia have been studied separately, or compared to high-dose fentanyl anesthesia in previous investigations utilizing a single infusion rate for each drug. Although hemodynamic stability during induction of anesthesia is usually characteristic of this technique, reports of hypotension in some patients following infusion of high-dose S raised concerns about administration safety. (1) In addition, S unlike fentanyl, caused myocardial depression in dogs. It would appear that various infusion rates and induction doses of S need to be studied to determine, if possible, an optimal combination which avoids hypotension during induction of anesthesia and hypertension secondary to surgical stimulation, i.e. sternotomy. The purpose of this study was to compare in a controlled manner hemodynamic profiles of three infusions of high-dose S anesthesia while holding the total administered induction dose constant. In addition, it was hoped that pharmacokinetic analysis would help explain any observed differences in pharmacodynamic effects between the study groups.

Methods: Institutional informed consent was obtained from all patients before enrollment in the study. Premedication consisted of morphine, diazepam, and valium. Chronic medications included nitroglycerin and small doses of beta or calcium channel blocking agents. Seventeen patients ages 51 to 76 years undergoing CABG surgery were randomly assigned to receive 15 mcg/kg of S administered with oxygen and a combination of metocurare and pancuronium for muscle relaxation over 0.5 min (Group A), at a rate of 5 mcg/kg/min (Group B), or at a rate of 2 mcg/kg/min (Group C). Patients with allergy to S, IDDM, poor LV function (Ejection Fx.<0.4), or fixed cardiac output were exluded. Monitoring of all patients included a five lead EKG (HR), oxygen saturation, mean arterial pressure (MAP), pulmonary artery pressure (MPAP), central venous pressure, pulmonary wedge pressure, cardiac index (CI), temperature and two lead EEG. The need to intervene with vasoactive, inotropic, or other anesthetic agents to correct changes in cardiovascular hemodynamics was documented. Blood samples were collected at 0.5, 1, 3, 5, 8, 30, 60 and 80 min following the start of the S infusion. Serum and cells were separated and stored at -20°C for future analysis. The compressed spectral array of the EEG was recorded to observe the lowest frequency and the time to the lowest frequency shift of the spectral edge. Statistical anaylsis of descriptive group characteristics was performed using Fisher's Exact and the Mann-Whitney tests. Hemodynamic variables were compared between groups using ANOVA and within groups using unpaired t tests. Statistical significance was defined by $p<0.05$.

Results: The three groups in this study were homogeneous in terms of age, gender distribution, weight, medications, and preoperative vital signs. Hemodynamic variables (mean ± SD) are presented in table 1 at specified intervals: Control, 1,5, and 10 min after starting the S infusion, before sternotomy (BS), and after sternotomy (AS). There were statistically significant differences between the groups for all variables, but changes in CI were not clinically significant. Although not statistically significant, HR decreased BS in all groups, but increased AS in group A only. A significant decrease in MAP occurred BS in group C. At one min MAP in group A decreased $(0.05<p<0.1)$. Neosynephrine was used in 3 of 6 patients each in groups A and C, but in none of the patients in group B. Supplemental anesthetics were not required during the study period.

Discussion: Comparison of hemodynamic variables between the three groups was likely valid as the composition of the groups was similar. Pharmacokinetic analyses of blood samples drawn during the three S infusions were not yet available. The trend in all groups during the study period was for a decrease in HR, MAP, and MPAP. The hypotension observed in group A and C patients (most rapid and slowest infusions studied) was due to reduced systemic vascular resistance, and was tolerated or easily corrected. However, such alterations may not be well tolerated by patients with ischemic or poorly functioning left ventricles. In contrast to the findings of a previous study (2), hypertension AS was not a problem in this investigation. Although none of the studied S infusion rates was free from unwanted cardiovascular hymodynamic effects, group B patients required the least pharmacologic intervention.

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TABLE 1.
TIME (min)

		Control	1	5	10	BS	AS
A*	HR	63±9	67±15	66±9	65±9	58±8	71±19
	MAP	91±10	74±21	83±20	84±17	83±11	80±10
	MPAP	19±3	16±3	16±2	15±2	14±5	14±6
	CI	3±1	3±1	3±0	3±0	3±1	2±0
B*	HR	75±20	79±25	78±21	75±19	59±13	71±20
	MAP	106±17	101±30	97±27	93±19	82±13	88±13
	MPAP	25±11	28±15	26±11	23±11	16±7	19±12
	CI	3±0	3±1	3±0	3±0	2±0	2±0
C*	HR	80±26	75±20	80±14	76±19	62±11	60±11
	MAP	98±10	93±32	90±13	84±19	82±6**	94±14
	MPAP	17±4	19±6	18±5	17±4	17±4	16±3
	CI	3±1	3±0	3±1	3±1	2±0	2±0

*p <0.05 between groups
**p<0.05 compared to Control

Title: ABSORPTION OF MIDAZOLAM BY THE SCI-MED MEMBRANE OXYGENATOR

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Introduction. High dose narcotic anesthesia during cardiac surgery is frequently supplemented with midazolam to prevent awareness and recall. Decrease in fentanyl plasma concentration during cardiopulmonary bypass (CPB) is a well recognized phenomenon and occurs in excess of the values predicted by dilution alone.[1] The site of fentanyl uptake by the CPB circuit was demonstrated to be the membrane oxygenator.[2] Monitoring of midazolam levels during CPB has not previously been reported. The purpose of this study was to evaluate the interaction of midazolam with the CPB circuit in vitro.

Methods. EXPERIMENT 1: A CPB circuit was assembled using 1/4" PVC tubing, a bubble trap and the Sci-med 0400-2A membrane oxygenator. The system was primed with 250ml of Normosol - R. Flow was maintained at 0.35 l/min. This study was performed at room temperature=$23^{o}C$. At time=0, a control sample was obtained. 25 mg of midazolam was then added (0.1 mg/ml). Aliquots were taken for midazolam analysis at the following times: 0.5, 5, 10, 15, 30, and 45 minutes. Midazolam levels were assayed in duplicate utilizing HPLC.[3] The entire experiment was repeated with a new circuit and a single variation. The second priming solution included fentanyl 2mcg/ml. The CPB system was circulated for 30 minutes prior to the addition of midazolam to allow for equilibration of fentanyl with the membrane.[2]

EXPERIMENT 2: This experiment employed tritiated midazolam. A solution was prepared containing Normosol-R (pH adjusted to 7.4) with midazolam 14 mcg/ml. 2ml of this solution was placed in each of 5 test tubes. A control sample was obtained from each tube at time 0. A 1cm^2 piece of membrane material was then placed into each of the test tubes. Solution samples were collected for midazolam levels after 30 sec then at five min intervals for one hr. Midazolam analysis was performed by liquid scintillation.

Results. The decreases in midazolam concentration with the intact CPB circuits are illustrated in Figure 1. 57% of the available midazolam was lost from the solution during the first pass through the membrane oxygenator. 83% of the midazolam was absorbed at 10 minutes and 92% was absorbed within the 45 minute study period. This is equivalent to a presumed uptake by the membrane of 5.7 mcg/cm^2 Prior saturation of the membrane with fentanyl did not alter subsequent absorption of midazolam.

The decrease in midazolam concentration with the isolated membrane squares is illustrated in figure 2. 63% of the initial midazolam in solution disappeared by 30 minutes. The plateau beginning at that time reflects a calculated membrane saturation of 11.0 ± 2.2 mcg/cm^2.

Discussion. This is the first study to demonstrate the potential for uptake of midazolam by the cardiopulmonary bypass circuit. The experiment utilizing samples of isolated membrane material demonstrates the specific ability of the Sci-med brand oxygenator for midazolam absorption. The calculated membrane uptake of drug/unit area was 5.7 mcg/cm^2 in the intact circuit studies and 11.0 mcg/cm^2 in the isolated membrane experiment. This discrepancy can be explained by one difference in methodology. In experiment 1, only 6.2 mcg/cm^2 was available for absorption. Whereas, in experiment 2, each square cm of membrane was exposed to 28.0 mcg of midazolam. The amount of midazolam available in solution was insufficient to saturate the membrane in experiment 1. The accuracy and validity of isolated membrane samples to reflect uptake by the intact CPB circuit has been previously reported for fentanyl.[2] Our results suggest that the CPB circuit will be saturated at a midazolam concentration of 11 mcg/cm^2. Prior saturation of the membrane with fentanyl did not alter absorption of midazolam.

The interaction of a patient with the CPB is a very complex clinical phenomenon. Although this study clearly shows invitro the potential for subtherapeutic plasma levels of anesthetic agent during CPB, further work is necessary before application of these findings to clinical practice. Many factors may modify this interaction including composition of the priming solution, temperature, concurrent use of other anesthetic agents, type/brand of oxygenator and type of CPB circuit tubing. The in-vivo occurence of subtherapeutic anesthetic concentrations associated with CPB may produce adverse physiologic and psychologic effects. Clinical studies are necessary to assess the effects of CPB on plasma midazolam levels.

References.

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FIGURE 1

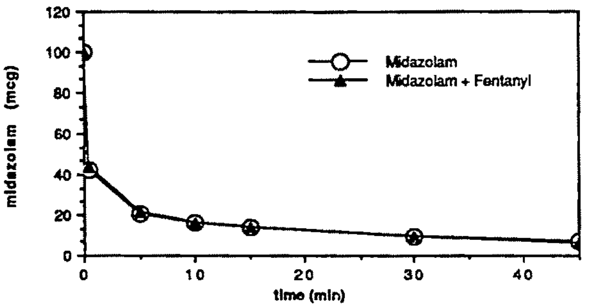

Fig 1: Fall in circulating midazolam level in intact CPB

FIGURE 2

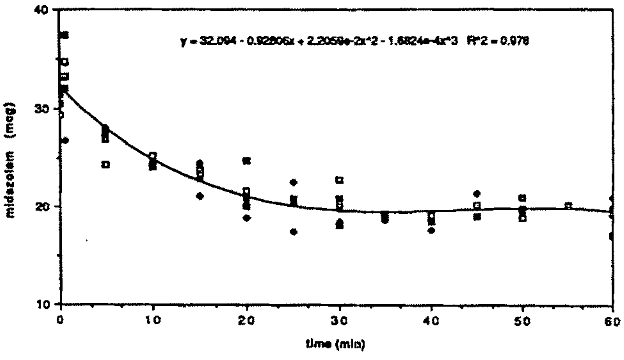

Fig 2: Fall in midazolam level with isolated squares

Title: EVALUATION OF ANESTHETIC DEPTH DURING OPEN HEART SURGERY

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Introduction. Presently, clinical, hemodynamic, electroencephalographic (EEG), or somatosensory evoked potential (SEP) measurements are used to assess depth of anesthesia. The responses to intraoperative stress that occur during periods of inappropriate anesthetic depth may correlate with increased post-operative morbidity[1] or awareness[2]. Recently, continuous monitoring of spontaneous and provoked lower esophageal contractility (LEC) has been shown to be useful for evaluating the depth of anesthesia[3]. The present study was designed to (1) evaluate the depth of anesthesia during open heart surgery (OHS) and hypothermic cardiopulmonary bypass (CPB) utilizing three anesthetic techniques, and (2) compare LEC with other signs of anesthetic depth.

Methods. With institutional approval and informed patient consents, measurements were performed on 33 patients for elective OHS. Patients premedicated with lorazepam (2-4 mg orally) were randomly assigned to one of three groups. Group A (n=11) received an induction dose of thiamylal sodium 2-4 mg/kg, I.V., and isoflurane (0.5-2.5% end-tidal concentration) for maintainence. Group B (n=11) received bolus injections of fentanyl (75-125 mcg/kg) for induction and maintainence. Group C (n=11) received a sleeping dose of fentanyl for induction and a continuous fentanyl infusion (5-15 mcg/kg/hr) for maintainence. Atracurium was used for muscle relaxation. All patients were ventilated with an FiO_2 of 1.0, and the end-tidal CO_2 was maintained at 38 ± 2 mmHg. Standard hemodynamic monitoring for OHS was utilized. In addition, the EEG was monitored using frontal and parietal leads bilaterally, and frequency was analyzed by spectral analysis. Median nerve SEPs were recorded over the brachial plexus and contralateral sensory cortex (N-19). The Neurotrac* spectral analyzer was used to monitor both the EEG and SEPs. Following intubation, a disposable balloon-tipped esophageal probe for the continuous monitoring of LEC was inserted and the data was displayed and recorded by the Lectron 302**. Total LEC activity was calculated as the esophageal contractility index (ECI); ECI = 70 x SLEC + PLEC. Measurements were compared at the following stages: (I) post-intubation; (II) sternotomy; (III) CPB Cooling, esophageal temperature (ET) 32-28 C; (IV) CPB with ET $<$ 25 C; (V) CPB Rewarming, ET 28-32 C; (VI) Post-CPB; and (VII) Sternal closure. The anesthesiologist was blinded to the EEG, SEP, and LEC monitoring. Data was analyzed by chi-square analysis, Student's t-test, and analysis of variance; a p value of less than 0.05 was regarded as significant.

Results. There were no significant differences in patient age, weight, CPB time, or length of surgery between groups A, B, and C. Shown in the Table are the number of patients who demonstrated inadequate anesthesia based on hemodynamic (MAP or HR $>20\%$), cerebral (EEG $> 20\%$ or SEP $< 20\%$), and LEC (ECI $>$ 50) criteria. Of 231 measured events of anesthetic depth in each group, the continuous infusion of fentanyl (group C) had significantly fewer inadequate anesthesia events (21/231) than either group A (39/231) or group B (46/231).

Discussion. The frequency and amplitude of lower esophageal contractions has been proposed as a correlate to anesthetic depth. During deep anesthesia there is little or no intrinsic esophageal activity, while during light anesthesia LEC is evident. LEC is not affected by skeletal muscle relaxants since the musculature of the lower half of the esophagus is nonstriated. The motor activity of the esophagus is predominantly controlled by brain stem nuclei and mediated by vagal pathways. It is assumed that the inhibitory effect of anesthesia upon LEC results from the central neurologic effect of the anesthetic agents.

The present study reveals that inadequate depth of anesthesia during OHS and CPB may be more common than previously appreciated. Our data suggests that a continuous infusion of fentanyl may provide superior control of anesthetic depth, thus decreasing the likelihood of intraoperative stress and awareness. Finally, it appears that monitoring of LEC may be a reliable and useful determinant of anesthetic adequacy under a variety of clinical conditions.

*Interspec, Inc., Philadelphia, PA

**American Antec, Inc., Valencia, CA

TABLE

Number of patients inadequately anesthetized by hemodynamic, cerebral, and LEC criteria.

Stage	I	II	III	IV	V	VI	VII	Total
Group A	8	5	7	3	2	8	6	39
Group B	7	8	4	5	4	9	9	46
Group C	5	4	5	2	2	1	2	21

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Title: ORAL H2-ANTAGONIST PROPHYLAXIS IN THE OUTPATIENT SETTING; RANITIDINE vs. FAMOTIDINE

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Introduction. The ambulatory surgical patient poses particular problems with respect to aspiration prophylaxis since anti-acid regimens usually involve dosing the night prior to surgery. We often must rely upon regimens administered less than two hours prior to anesthetic induction. Unless a gastroprokinetic agent is administered at this time, a rapid reduction in gastric volume is unpredictable. The present study compared the rate of pH change after reportedly equipotent doses of the H2-antagonists, ranitidine (Zantac) and famotidine (Pepcid), on the morning of ambulatory surgery.

Methods. After institutional approval had been obtained, two hundred and ten (n=210) ASA I - III patients scheduled for general endotracheal anesthesia were enlisted for study. Exclusion criteria were gastrointestinal disease, pregnancy, asthma or a systemic condition that might affect GI acidity or motility. Patients were assigned to receive either: no medication (140 controls); or famotidine 40 mg PO (n=70) or ranitidine 300 mg(n=70) PO with 15 ml of water 30-120 minutes prior to surgery. Treated patients were grouped according to the dose-sampling interval: 1) 30-45 min; 2) 46-60 minutes; 3) 61-75 min; 4) 76-90 min; 5) greater than 90 min. There was no attempt to regulate the time interval, which was determined by the operating room schedule. Following induction with fentanyl, midazolam, thiopental and muscle relaxant, anesthesia was maintained with oxygen, nitrous oxide and halogenated agent. Within 10 minutes of intubation, an orogastric tube was passed into the stomach, and its position was confirmed by auscultation. At this time, the stomach contents were aspirated in a uniform manner into a suction trap. The aspirate was assessed for volume and pH. The latter was determined with commercial pH paper, whose reliability was previously documented (1). Data in each group was expressed as mean ± standard deviation. Overall time effects were analyzed by ANOVA; specific time intervals were compared with the Duncan Multiple Range Test. Mean differences between treatment groups were compared by t-test while the incidences of low pH were compared with Fischer's exact test. $p<0.05$ was considered to be significant.

Results. Control pH averaged 1.6+1.0; all control subjects had a pH below 2.5. Beyond 60 minutes, 3/38 ranitidine and 10/38 famotidine patients still had a pH<2.5. Beyond 70 minutes, 0/32 patients in the ranitidine group and 4/39 in the famotidine group had pH<2.5 (p=ns by Fischer's exact two-tailed test). After 105 minutes, gastric pH was greater than 2.5 in all patients having received study medication. A significant time effect was noted for both ranitidine and famotidine ($p<0.05$ by ANOVA). However, the mean±SD for each time group (Table 1) were not always equivalent. By 30-45 min after ranitidine, there was a significant difference from control ($p<0.05$ by the Duncan Multiple Range Test). At 30-45 min, the ranitidine group's pH was significantly greater than that following famotidine ($p<0.05$ by t-test). For the latter a significant difference from control was not noted until 46-60 minutes after dosing. After either medication, gastric volume did not change significantly (p=ns).

Discussion. Since oral dosing costs approximately 20% of IV administration, the present confirmation of the efficacy of oral H2-antagonist therapy given on the morning of surgery suggests that pretreatment with an oral H2-antagonist is very reasonable from a cost-benefit standpoint. A typical oral dosage costs; Ranitidine (150 mg) $1.10 and Famotidine (20 mg) $.85 while the intravenous form costs; Ranitidine (50 mg) $4.00 and Famotidine (20 mg) $5.93. In the 140 treated patients, this would amount to a cost difference of; $230 for Ranitidine and $355 for Famotidine. Furthermore, oral therapy can be administered without the need for an established IV route. Within 75 minutes of oral ranitidine, virtually all healthy ambulatory surgical patients had effective neutralization of gastric pH. At an equipotent dose, a slightly longer time to effectiveness was required after famotidine administration. Perhaps even higher doses would accelerate onset. It remains to be seen if patients at higher risk for aspiration will have a similar time course or whether night-time dosing and/or a gastroprokinetic agent should be included in their preoperative regimen.

Table

	pH vs Dose-Sampling Interval (min)					
	0	30-45	46-60	61-75	76-90	≥90
none	1.6±1	-	-	-	-	-
Ran	-	3.3±2	4.0±2	4.7±2	6.3±2	6.2±1
Fam	-	1.6±1	2.6±2	4.4±2	4.8±2	6.3±2

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Title: A COMPARISON OF SERUM LIDOCAINE LEVELS USING TWO VARIATIONS OF THE AXILLARY BLOCK

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Introduction. Variations of the axillary approach have been used successfully to block the brachial plexus. These include the elicitation of a parethesia, transarterial fixation, and the perivascular (Winnie) technique(1). Complications of the transarterial technique include hematoma, retrograde flow with local anesthetic systemic toxicity(2), and vascular insufficiency with epinephrine(3). Since the artery is not violated using the perivascular technique, the absorption of local anesthetic with concomittant systemic toxicity should be minimal. In our study, we attempted to show a difference in absorption of local anesthetic between these two techniques.

Methods. Approval was obtained from our Human Investigation Committee. In addition, we obtained written informed consent from each patient. A total of 16 patients, physical status (ASA) I-III, were examined. These patients had elective surgery to the forearm, elbow, or hand. They were randomized into two groups. Group A (N=7) received axillary block via transarterial fixation while group B (N=9) received a perivascular block, utilizing the Winnie method of fascial "pop". Both were single injection techniques. Each of the patients was premedicated with diazepam, 5-10mg P.O. The blocks were performed with a 22 gauge short B-bevel needle. Lidocaine (1%), 40ml/70kg was injected. No epinephrine was used. A ring block using 2-3cc of 1% lidocaine was performed over the axilla to block the intercostobrachial nerve. Time zero was defined when the injection was completed. Serum lidocaine samples were obtained from a catheter in the contralateral arm at intervals of 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, and 240 minutes. Age and sex were recorded. Peak serum concentration and time to peak absorption were measured. Absorption and elimination rate constants were calculated for each patient utilizing a one compartment pharmacokinetic model(4). A Student t-test was used to evaluate any statistical difference for peak levels and absorption times between the groups.

Results. All blocks provided adequate surgical anesthesia and there were no signs of systemic toxicity, hematoma, or vascular insufficiency. The mean peak serum lidocaine level was 3.2 ± 0.4 ug/ml for the transarterial group and 3.5 ± 0.3 ug/ml for the perivascular group. The time to reach peak plasma level was 12 ± 2.3 minutes for the transarterial group and 15 ± 1.7 minutes for the perivascular group. Statistical treatment of the data showed no significant difference between the groups ($p<0.05$) with reference to peak absorption time and concentration.

Discussion. We conclude that with reference to systemic absorption and local anesthetic toxicity, there is no difference between the transarterial and perivascular techniques. Therefore, selection of either technique on the basis of reduced systemic absorption is not warranted by our findings.

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TABLE

GROUP	Cmax(ug/ml)	Tp(min)	Te(min)
Perivascular	3.5±0.3*	15±1.7*	174±41*
Transarterial	3.2±0.4*	12±2.3*	115±29*

Cmax=Peak serum level
Tp=Peak absorption time
Te=Elimination half-life

*Denotes standard error of the mean

Title: EFFECTS OF OPIOID REVERSAL ON PULMONARY CAPILLARY PERMEABILITY

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Introduction. Naloxone reversal of opioid anesthesia has been known to cause pulmonary edema in certain patients[1,2]. The pathophysiology underlying this phenomenon is unknown. We studied the effect of naloxone alone and fentanyl reversal on the pulmonary capillary pressure and pulmonary lymph flow in dogs.

Methods. Adult mongrel dogs weighing 20 to 30 kg were anesthetized with thiamylal, intubated, and ventilated with 0.5-1.0% halothane in oxygen using a volume respirator. A pulmonary artery catheter was inserted via the left internal jugular vein. Pulmonary capillary pressure was determined by analyzing the pressure transient following inflation of the balloon in the pulmonary artery catheter[3]. Arterial pressure was measured utilizing a femoral artery catheter. A left thoracotomy was performed and a lymphatic efferent of the bronchial lymph node was cannulated. Two sets of experiments were performed. In the first experiment, naloxone 0.01mg/kg/min was infused following a minimum 2 hour baseline period. In the second experiment a baseline 2 hour period was followed by infusion of fentanyl 20ug/kg. The animals were monitored for 30-60 minutes following which an infusion of naloxone 0.01mg/kg/min was begun. Pulmonary arterial and systemic arterial pressures and heart rate were monitored continuously. Lymph flow (Q_L), lymph protein concentration, and pulmonary capillary pressure (P_C) were measured at fifteen minute intervals. The data were analyzed using analysis of variance for repeated measurements.

Results. Naloxone alone produced no significant change in Q_L, lymph protein concentration, or P_C. However, following fentanyl reversal by naloxone, there was a significant increase in Q_L ($p < 0.001$) while lymph protein concentration and P_C remained stable (Table 1).

Discussion. The Starling equation implies that pulmonary edema must develop from a change in hydrostatic pressure, a change in oncotic pressure, or a change in vascular permeability[4]. Changes in lung vascular permeability can be implied from changes in lymph flow and lymph protein concentrations if pulmonary capillary pressure remains constant[5]. The results of this experiment suggest that while naloxone alone does not change pulmonary capillary permeability, fentanyl reversal by naloxone increases the flow of lymph without significantly changing lymph protein concentration or the lymph/plasma protein ratio. Our data consistently points towards an increase in pulmonary capillary permeability, thus representing the first potential pathophysiologic explanation of opioid reversal pulmonary edema.

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Table 1.

Means ± SEM of Reversal of Fentanyl by Naloxone

	Control	Time after fentanyl reversal (min) 15	30	45	60
QL (ml/min)	0.033 ±.002	0.075 ±.004	0.055 ±.005	0.060 ±.004	0.056 ±.006
Lymph protein (g/dl)	3.83 ±.20	3.60 ±.06	3.63 ±.09	3.67 ±.17	3.67 ±.17
Pc (mmHg)	5.1 ±1.0	7.67 ±1.8	5.7 ±1.5	5.3 ±1.2	5.7 ±1.2

Title: HELIUM DOES NOT REDUCE ENDOTRACHEAL TUBE FLAMMABILITY

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Introduction. Endotracheal tube (ETT) fires continue to present a danger to patients undergoing procedures involving the use of airway laser or cautery. Recently (1), we introduced the concept of using the oxidant O_2 index of flammability to compare the flammability of the various ETT's in oxygen (O_2)/nitrogen (N_2) environments. There have been several reports (2) recommending the use of helium (He) rather than N_2, as the diluent for O_2 to decrease ETT ignitability. This study measures the flammability of polyvinylchloride (PVC), red rubber (RR), and silicone (Si) ETT's in O_2/He atmospheres by use of the oxidant O_2 (He) index of flammability.

Materials and Methods. Using a method similar to the one previously described (1) gases (O_2, N_2, He) were routed from tanks through a mixing chamber and then into the test cylinder. ETT's to be tested were supported within the cylinder. Oxygen concentrations were measured with a paramagnetic gas analyzer (Puritan Bennett, Wilmington, MA). Ignition was accomplished with a propane flame. Initially, ignition was attempted in O_2/He, but was unsuccessful at O_2 concentrations less than 40%. Therefore the ETT tested was first ignited in O_2/N_2 and then the N_2 was abruptly replaced by He. Helium concentrations were then increased (decreasing O_2 concentrations) slowly, until a candle like flame was just maintained on the ETT. The oxygen concentration at this point (with He diluent) was defined as the oxidant O_2 (He) index for that particular ETT. The above was repeated five times for each type of ETT tested. The oxidant O_2 (He) index for each type of ETT was determined by averaging the five determinations (mean ± SD) and calculating the respective 99% confidence intervals for each tube type. Results with helium were compared to our previous results with nitrogen (1) by drawing the 99% confidence interval around the standard error of the difference between each set of means.

Results. The oxidant O_2 (He) indices of flammability for the three types of ETT's are presented in table 1. For comparison, table 2 lists the previously reported (1) corresponding oxidant O_2 (N_2) indices for the three types of ETT's.

Table 1. Oxidant O_2 (He) indices of flammability.

	Index	99% Confidence Limit
PVC	.263 (± .010)	± 0.016
RR	.194 (± .009)	± 0.018
Si	.194 (± .005)	± 0.011

Table 2. Oxidant O_2 (N_2) indices of flammability.

	Index	99% Confidence Limit
PVC	0.263 (± .004)	± .005
RR	0.176 (± .003)	± .003
Si	0.189 (± .009)	± .01

The 99% confidence interval for the standard error of the difference between means (N_2 vs He) are: PVC 0.019, RR 0.018, Si 0.022. One can be 99% confident that the real differences between these means are no greater than the observed differences ± these amounts. The inference here is that there are no practical differences between these means, and for PVC & RR any absolute differences are probably smaller than could be readily measured (as within the margin of measurement error).

Discussion. Fire is dependent on three variables: ignition source, fuel and oxidizing environment. Ignition sources in the operating room include laser, electrocautery, high speed drills, etc. The precise amount of ignition energy delivered is difficult to define and is dependent on many variables; i.e., focal point of laser, energy of laser or cautery, reflection of energy via metal instruments, absorbtion of energy by surrounding tissues, etc. Flammability for a given fuel however, is only dependent on the oxidizing environment as measured by the oxidant O_2 index, and is independent of ignition source or energy (1). This study demonstrates that the flammability of ETT's in oxygen with nitrogen as the diluent is similar to the flammability of the ETT's in oxygen with helium as the diluent. This suggests that helium may not be protective when used as a diluent. We did confirm the difficulty of igniting ETT's in concentrations of O_2 less than 40% (He diluent) with a propane flame. However once ignited, He will not retard flammability. Since ignition is unpredictable and difficult to quantitate one must not be lulled into a false sense of security with the use of helium. ETT contact with maximal ignition energy may occur and a flame may be propagated in helium. Once propagated, flammability will be no different than that seen with O_2/N_2.

We therefore question the validity of the practice of substituting He for N_2 as an O_2 diluent, since this study demonstrates no change in ETT flammability.

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Title: OXYMORPHONE ADMINISTERED VIA BASAL INFUSION PLUS PCA IN POST-CESAREAN DELIVERY PATIENTS

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INTRODUCTION. Patient controlled analgesia (PCA) has been shown to provide useful post-operative analgesia and high patient satisfaction. Its effectiveness, however, seems to be diminished during periods of sleep, as reductions in PCA boluses often result in sub-analgesic plasma concentrations of narcotic. The need for frequent incremental dosing upon reawakening and lack of analgesic uniformity observed with conventional PCA prompted us to evaluate a new means for achieving more consistent pain relief. We postulated that the addition of a sub-therapeutic basal narcotic infusion (BI) would increase the overall efficacy of PCA by maintaining effective analgesia even after a prolonged period of sleep. The following evaluation compares the analgesic effectiveness and adverse effects observed when the rapid-acting opioid analgesic oxymorphone[1] is administered via BI+PCA or PCA alone.

METHODS. Following institutional approval, written informed consent was obtained from 34 patients undergoing elective cesarean delivery. Epidural anesthesia was provided for surgery using 2% lidocaine with epinephrine 1:200,000 to obtain a T4 sensory level. Patients were divided into two groups, with patients in each group receiving a 1 mg "loading" dose of oxymorphone in the Recovery Room (PAR) when they first complained of pain. Patients in Group 1 (n=18) received traditional PCA, utilizing oxymorphone (0.3 mg/bolus, 8 min lockout, 6 doses/hr maximum). Patients in Group 2 (n=16) were placed on an infusion pump (Pharmacia-Deltec, CADD-PCA) programmed to administer a BI of 0.1 mg/hr oxymorphone with superimposed PCA boluses (0.3 mg/bolus, 8 min lockout, 5 doses/hr maximum).

Patients were discharged from the PAR and observed every 2 hrs for 24 hrs by a trained nurse observer. Data collected included: a) pain scores using a 10 cm visual analogue scale (VAS) (0 = no pain; 10 = worst possible pain) at rest as well as upon sitting up and dangling legs; b) Patient satisfaction (0 = no satisfaction; 10 = complete satisfaction); c) Number of boluses and total 24 hr dose administered; d) Incidence and degree of nausea/vomiting, pruritus, sedation, respiratory depression, and need for concomitant medication. Data are presented as mean ± SD. Results were analyzed by unpaired t test, with a p value of 0.05 or less considered significant.

RESULTS. Patients receiving BI+PCA consistently achieved more effective analgesia than those receiving PCA alone (Fig. 1). Group II VAS pain scores were significantly lower at rest (1.0±0.5 vs 2.2±1.4, $p < 0.05$) and with movement (2.2±1.2 vs 4.0±1.8, $p < 0.05$). This superior level of analgesia was achieved at a lower total 24 hour dosage (14.5±2.4 mg in Group II vs 17.0±2.7 mg in Group I).

The incidence of nausea was appreciable in both groups but significantly greater in patients who received BI+PCA (23% vs 44%, $p < 0.05$). In all cases, this responded promptly to droperidol 0.625 mg IV. Despite differences in analgesia and incidence of nausea, there were no significant differences in mean patient satisfaction scores between groups (PCA 8.9, BI+PCA 9.1). Respiratory depression requiring treatment was not observed.

DISCUSSION. BI+PCA provided superior post-operative analgesia at rest and during movement when compared with patients who received PCA alone. Moreover, this form of parenteral analgesic therapy achieved pain relief and satisfaction scores equivalent to that previously noted at our institution only with epidurally administered opioids[2]. This improvement in pain scores was accomplished with reduced 24 hr dose requirements, suggesting a more efficient delivery of narcotic which may be attributed to more uniform plasma levels of drug. While BI+PCA was associated with a higher incidence of nausea and vomiting, patient satisfaction remained extremely high, possibly reflecting the effectiveness of anti-emetic therapy with droperidol. Thus, it appears that BI+PCA can provide a superior form of intravenous analgesia; however, different opioids and basal infusion rates, as well as anti-emetic prophylaxis, should be evaluated so as to minimize nausea and further increase patient satisfaction.

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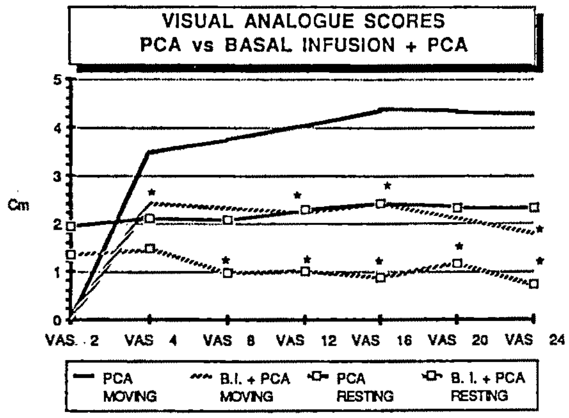

Figure 1: Visual analogue scores (cm) plotted against time (hours) on PCA. *BI+PCA significantly lower than PCA, $p < 0.02$

Title: EFFECT OF LABETALOL ON HEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION IN HYPERTENSIVE PATIENTS

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Introduction. Acute blood pressure (BP) elevation in hypertensive patients prior to induction of anesthesia is common. Prys Roberts (1) reported a high incidence of an exaggerated response of tachycardia and hypertension--in hypertensive patients following endotracheal intubation. Labetalol (LAB) has been shown to effectively attenuate tachycardia and hypertension associated with endotracheal intubation (INT) in normotensive patients. Use of Beta-blockers in chronic hypertensive patients immediately before induction of anesthesia is controversial (1, 2, 3). This randomized double blind study was designed to evaluate the effectiveness of preinduction IV LAB given to hypertensive patients to attenuate and prevent the hyperdynamic response to INT.

Methods. The study was approved by the Review Board and informed consent was obtained from each patient. Ninety-six hypertensive patients scheduled for elective surgery were screened. Patients with contraindications to beta blockers were excluded from the study. Twenty patients who developed elevated BP prior to induction of anesthesia (SBP 170 mmHg and/or DBP 100 mmHg) were selected for study and randomized to receive either LAB (Group L) or placebo (Group P). Those fifteen patients who were receiving antihypertensive therapy were maintained on their standard regimen. Monitoring include ECG, automatic BP cuff (Dinamap), endtidal CO_2 and O_2 saturation. Before induction of anesthesia, 10 mg. of LAB was administered as a bolus followed by 10 mg. increments every 5 minutes to either lower SBP 20% from baseline and/or lower DBP 100 mmHg. A maximum total dose of 1 mg./kg. was not exceeded. Anesthesia was induced with fentanyl 0.2 mg./kg., pentothal 4 mg./kg., and succinylcholine 1 mg./kg. After INT, anesthesia was maintained using N_2O-O_2 (70:30) mixed with enflurane. Vecuronium was used for muscle relaxation. BP and HR were recorded every 2 minutes during induction of anesthesia and INT than every 5 minutes. Data was analyzed with ANOVA for repeated measurements with p 0.05 considered significant.

Results. Table I represents hemodynamic data. LAB (averaged dosage 0.5 mg./kg.) significantly decreased SBP, DBP, HR, and RPP prior to induction of anesthesia and blunted the stress response to INT (p 0.05). Pressure reduction was accomplished smoothly, and this effect was maintained during surgery which lasted at least 2 hours. In Group P, there was only a moderate, non-significant decrease in BP and HR prior to INT. Following INT, there was a transient increase in HP and RPP (p 0.005). However, three patients in this group, not treated preoperatively for hypertension, developed significant rises in SBP 210 mmHg and HR 120 b/min. In Group P, there were significant fluctuations in BP during surgery requiring more enflurane anesthesia to attenuate hemodynamic changes in response to surgical stimuli. No patients became hypotensive, bradycardic or developed bronchospasm following administration of LAB.

Discussion. The combination of preinduction sedative/narcotic with small incremental doses of IV LAB may be an ideal combination of drugs to safely and effectively blunt the hemodynamic response of anesthetic induction and tracheal intubation in hypertensive patients. Preinduction LAB is especially indicated in hypertensive patients inadequately treated for hypertension preoperatively.

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Table I

		Baseline	Before induction	AFTER INT		
				30 sec.	3 min.	5 min.
SBP mmHg	L	197±12.5	167±12.3#*	153±22.6	147±13.3	144±14.4*
	P	191±14.2	185±19.5	170±33.9	150±38.2*	160±29*
DBP mmHg	L	107±7.2	94±7.9*	87±5.2*	81±7.6*	81±9.2*
	P	94±15.9	98±10.5	92±22.2	30.5±23.2	78±17.6
HR	L	83±9.8	81±10.9	77±9.1*	75±8.3*	71±5.7*
	P	82±16.1	87.5±10.3	92.9±14.6*	37.6±14.6	81±18.5
RPP No X 10^3	L	18.4±2.2	13.6±2.4*	12.1±2.4#*	11.1±1.9*	10.2±1.0*
	P	15.6±3.1	16±2.0	16.4±4.0	13.2±3.6	12.8±3.6*

Mean Values ± S.D.

* p 0.05 within group

# p 0.05 between groups

Title: INTRINSIC PEEP DURING ONE-LUNG VENTILATION

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Introduction. Intrinsic positive end expiratory pressure (PEEPi) has been documented in ventilated patients with respiratory failure who have a persistant end expiratory flow (EEF) (1). EEF has also been noted during one-lung ventilation (OLV) for thoracic surgery (2). Since the application of extrinsic PEEP(PEEPe) has been suggested to improve arterial oxygenation during OLV (3), this study was performed to document the presence of PEEPi during OLV and the interaction of PEEPi and PEEPe on the total PEEP(PEEPt) developed during OLV.

Methods. Ten patients undergoing elective thoracotomy with OLV were studied after ethics committee approval and written informed consent was obtained. Spirometry (FEV_1 and FVC) was obtained pre-operatively. After induction of general anesthesia patients were intubated with a left-sided Mallinckrodt double-lumen endobronchial tube (#35-41Fr.) and its position verified fiberoptically. Patients were ventilated with a Seimans servo 900B ventilator at a constant tidal volume of 10ml/kg and a rate of 10 breaths/min for both two-lung ventilation (2LV) and OLV. Isoflurane in oxygen was used to provide anaesthesia and > 95% depression of muscle twitch maintained with pancuronium.

Measurements were made in the lateral decubitus position with the non-dependant hemi-thorax open. OLV was to the dependant lung. At the end of a normal expiration, the airway was occluded for six seconds. End expiratory flow (EEF) immediately prior to occlusion and the plateau airway pressure (Paw) during occlusion were recorded on a Hewlett-Packard 7754B four-channel recorder. The accuracy of the EEF and Paw measurements were verified with a Timeter calibration analyser (Timeter Instrument Corp., Lancaster, Penn.). PEEPe was provided by a spring-loaded 5cm PEEP valve (Vital Signs Inc., Totawa, N.J.). Measurements were made during 3 modes of ventilation in order: 2LV, OLV, and OLV plus 5cm PEEPe. For each mode of ventilation measurements were made at 3 different expiratory times (Te): (4.5, 3.9 and 2.4 sec) in random order.

The mean values of PEEPt for all 10 patients during 2LV, OLV, and OLV plus PEEPe were compared using Student's T-test for paired data. The correlation between PEEPi during OLV and EEF, age, and FEV_1 and FVC ratio was assessed using Pearson's Correlation Coefficient. The correlation between PEEPi and Te was assessed by linear regression analysis.

Results. The mean age of the patients (± S.D.) was 63 ± 15 years. 8 patients had right-sided thoracotomies. The mean PEEPt values for all patients at each Te are shown in the figure.

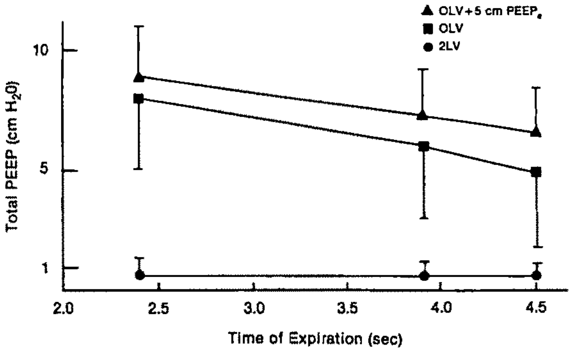

Figure: Mean total PEEP (± S.D.) versus expiratory time. OLV = one-lung ventilation, 2LV = two-lung ventilation

At an inspiratory/expiratory ratio of 1:3 (Te = 4.5 sec) mean PEEPt (without added PEEPe) was $0.5 cmH_2O$ during 2LV. This increased to 4.9cm during OLV and increased further to 6.5cm when 5cm PEEPe was added. The mean PEEPt was significantly greater during OLV than 2LV ($p<.01$) at each Te studied. PEEPt during OLV correlated significantly with the patient's age (correl. coeffic. = .75, p=.01) but not with EEF, FEV_1, or FEV_1/FVC ratio. During OLV, PEEPt was significantly higher with PEEPe than without at each Te ($p<.05$). There was a significant inverse correlation between PEEPt and Te ($p<.05$) during OLV.

Discussion: Significant intrinsic PEEP developes during OLV. When PEEPe is added during OLV the resultant PEEPt is increased. However, the increase is less than the value of the PEEPe itself. The presence of PEEPi should be appreciated whenever the use of PEEPe is considered during OLV. The hemodynamic and gas-exchange consequences of PEEPi during OLV remain to be studied.

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Title: A COMPARISON OF FIVE METALLIC TAPES FOR PROTECTION OF ENDOTRACHEAL TUBES FROM THE Nd-YAG LASER

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Introduction

The Neodymium-Yttrium-Aluminum-Garnet (N-d YAG) laser is used in a variety of surgical procedures including gynecologic, neurologic, and otolaryngologic surgery. A catastrophic complication reported with the use of this laser during airway surgery is ignition of the endotracheal tube.(1) No endotracheal tube has yet been found to be safe for use with the Nd-YAG laser at high power.(2) This study was undertaken to determine if five commercially available metallic adhesive tapes, applied to 8.0 mm ID Rusch (W. Germany) red rubber (RR) endotracheal (ET) tubes, could prevent Nd-YAG laser ignition of the tubes within 60s.

Methods

The five RR tubes were wrapped in an overlapping spiral fashion with 1/4-in wide metallic tape beginning at the cuffed end of the tube. A second segment of each tube was wrapped with the same tape but with its adhesive side outward. The tapes used were: 1. Radio Shack #44-1155 (Tandy Copr., Ft. Worth, TX) tape; 2. 3M #425 (3M Corp., Minneapolis, MN) aluminum tape; 3. 3M #433 aluminum tape; 4. 3M #1430 aluminum tape; and 5. copper foil tape (1mm-thick) (Venture Tape Corp., Rockland, MA).

A Lasersonics (Santa Clara, CA) model 1700 CO_2/Nd-YAG laser, in the Nd-YAG mode, with a hand-held laser probe was used. The laser output was set at 50W in the continuous mode, with a beam diameter of 0.70mm. The beam was directed perpendicularly at the shafts of the foil-wrapped tubes, through which 5 1/m of $O_2$was passed. The laser was continued until vigorous combustion was noted or up to a maximum of 60s. A "blowtorch" fire, if observed, was noted.

Results

Combustion and a blowtorch fire occurred in 6 and 15 sec, respectively, after laser contact with Radio Shack #44-1155 tape. Its reverse side was not tested. 3M #425 aluminum tape withstood 60s of laser emission without any effect. When its adhesive side was struck, smoking was noted immediately and at 60 s, tube combustion was noted beneath the tape. 3M #433 aluminum tape withstood 60s of laser radiation. When its adhesive side was exposed, it burned immediately, and a blowtorch fire was observed after 12 seconds. 3M #1430 aluminum tape allowed combustion immediately after laser exposure to either side. The laser was discontinued after vigorous flames were observed, and the flames were extinguished, so no blowtorch effect was noted. Lastly, Venture copper foil tape was not visibly changed after one minute of laser radiation. Smoking was noted after 5s and flames in 15s when the reverse side was struck with the laser.

Discussion

3M #425 aluminum tape afforded the best protection from Nd-YAG laser-induced ET tube combustion. Radio Shack #44-1155 and 3M #1430 metallic tapes offered essentially no protection from combustion induced by the Nd-YAG laser. 3M #433 aluminum and Venture copper foil tape were only warmed slightly when exposed to 60s of Nd-YAG radiation on their non-adhesive sides; however they did not prevent rapid, laser-induced combustion when their adhesive sides were exposed. Thus they offer an intermediate degree of protection from laser-induced combustion of ET tubes, since laser radiation could conceivably impinge on their adhesive.

In common with the present study, previous work(3) has demonstrated that Radio Shack 344-1155 tape and 3M #1430 tape offer little protection from the 70W, continuous CO_2 laser and readily combusted. Also, after exposure to 70W CO_2 laser radiation, as in the present study, the 3M #425, 3M #433, and Venture 1mm copper foil tape, were unaffected. The backing of Radio Shack #44-1155 and 3M #433 tape are flammable on exposure to either CO_2 or Nd-YAG laser radiation.(3) Venture copper foil tape's adhesive backing smoked but did not flame, and was not penetrated by the 70W-CO_2 laser. The Nd-YAG laser, in contrast, rapidly ignited its adhesive backing and penetrated the tape.

Our conclusions differ from those of Geffin, et al.(2), who noted RR ET tubes were not protected from Nd-YAG laser-induced combustion by aluminum foil tape. Geffin, et al., however tested only one type of tape (Radio Shack #49-502). In our study three of the five tapes tested offered significant protection against 50W Nd-YAG laser radiation. Thus, we have found an acceptable means to reduce the risk of direct ET tube combustion from the Nd-YAG laser.

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Title: A COMPARISON OF SPECIAL ENDOTRACHEAL TUBES FOR USE WITH THE Nd-YAG LASER

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The neodymium-yttrium-aluminum-garnet (Nd-YAG) laser is being utilized increasingly for surgery. It is especially useful for the treatment of obstructing tracheobronchial tumors. A report on endotracheal tube flammability with the Nd-YAG laser concluded that all the tubes tested were vulnerable.[1] A life endangering tube fire may result. This study was initiated to see whether a safe endotracheal tube for use with the Nd-YAG could be found.

Methods

A Lasersonics (Santa Clara, CA) model 1700 CO_2-Nd-YAG laser in the Nd-YAG mode and Zeiss operating microscope with a 400 mm lens were used. The laser's output was set to 50 watts in the continuous mode of operation with a beam diameter of 0.68 mm. The laser was directed perpendicularly onto the shafts of six different endotracheal tubes which had 5 L/min of oxygen flowing through them. The laser's emission was continued for one minute or until combustion occurred. The tubes used were: 1. A Rusch (W. Germany) red rubber(RR) tube. 2. A RR tube wrapped with 3M (St. Paul, MN) #425 aluminum foil tape. 3. A RR tube wrapped with copper foil tape (Venture Tape Corp., Rockland, MA). 4. A Bivonia (Gary, IN) Fome-Cuf$^{(R)}$ 6.0 mm ID laser endotracheal tube. 5. A Mallinckrodt laser-Flex^{TM} 6.0 mm ID tracheal tube. 6. A Xomed (Jacksonville, FL) Laser-shield^{TM} size 6 mm ID endotracheal tube. Tubes number 1 and 4 had the laser directed at an unmarked portion of the tube. The metallic foils used were wrapped in an overlapping spiral manner starting just above the cuffed end of the tube with a single piece of tape.

Results

Within 1 sec, the bare RR tube was penetrated. A blowtorch fire occurred at 13 seconds, however the tube remained in one piece. The RR tubes wrapped with the 3M #425 or copper tape suffered no damage from 1 min of laser fire. Smoke was noted at the site of laser impact within 1 sec with Bivona tube. A fire occurred by 12 sec, however the tube remained in 1 piece and no blowtorch fire occurred. Flames were noted by 1 sec at the point of the laser's impact onto the Xomed tube. The tube broke into several pieces with considerable flaming by 12 sec. Even after stopping the laser and turning off the oxygen supply, this tube fire was very difficult to extinguish.

Discussion

The use of the Nd-YAG laser in common with the CO_2 laser, may place the surgeon and anesthesiologist in competition for the airway. The high energy density delivered by the laser in proximity to combustible materials such as an endotracheal tube has caused catastrophic airway fires. An airway fire with the Nd-YAG laser has been described.[2]

The Nd-YAG laser emits radiation at 1064 nm in the infrared region, and is invisible. It has better hemostatic properties, and penetrates more deeply than the CO_2 laser. It can be conducted through a fiberoptic fiber. It has been useful for endoscopic resection of obstructing lesions of the major airways in patients usually under general anesthesia.

Geffin et al.[1] in an evaluation of tracheal tubes for use with the Nd-YAG laser found that all the tubes they tested were vulnerable to the Nd-YAG laser. They state "Although reflective aluminum tape was effective in protecting tubes from exposure to the CO_2 laser, the tape offered no protection from the Nd-YAG laser." However, they only evaluated one type of aluminum tape (Radio Shack #49-502). Our results using copper foil or 3M #425 aluminum foil tapes demonstrate that they provide the only effective protection of combustible endotracheal tubes from the Nd-YAG laser to date. Our findings showing that the RR and Xomed Laser-shield^{TM} were quickly penetrated by the Nd-YAG laser are consistent with those of Geffin et al.[1]

None of the special endotracheal tubes manufactured for use with the laser used in this study could withstand the impact of the Nd-YAG laser. These tubes are not, however, recommended by their manufacturers for use with the Nd-YAG laser. Our results showing that 3M #425 aluminum foil tape or copper foil tape provides complete protection against the direct impact of the Nd-YAG laser should provide clinicians with a simple, inexpensive and safe anesthetic technique for Nd-YAG laser endoscopic surgery.

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Title: AUTOLOGOUS BLOOD DONATION SERVICE FOR HIGH-RISK PATIENTS

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Introduction. With the onset of the AIDS crisis, public pressure has increased the utilization of autologous blood products. Such blood donations from ASA I or II patients are routinely collected in the blood bank. Since 5 percent of healthy individuals develop vaso-vagal symptoms on routine blood donation (1), blood banks have previously refused to allow donations by persons having significant cardiovascular disease. Blood bank personnel are not trained or experienced in resuscitation especially for patients with major cardiovascular disease. A large segment of the population now undergoing elective surgery is elderly and therefore carries a significant incidence of cardiovascular disease. To allow these patients the advantages of autologous blood utilization, a model program was developed in cooperation with the Departments of Anesthesia and Blood Banking.

Development and Program Outline:

Patients are referred to the blood bank for autologous blood donation by their surgeon. Blood bank personnel obtain a history and classify the patients to determine whether they may donate in the blood bank or in the "high risk program". Those classified as "high risk" have: 1) severe or poorly controlled hypertension, 2) angina or previous myocardial infarction, 3) congestive heart failure or valvular heart disease, 4) dysrhythmia, 5) aortic aneurysm, 6) seizure disorder or 7) previous cerebral vascular insufficiency. Patients are scheduled by the blood bank and admitted as outpatients one morning a week to the post anesthesia care unit (PACU). The PACU is utilized because of the presence of monitoring and resuscitation equipment. After reclining in donor chairs and having their hematocrits checked patients are monitored with a non-invasive blood pressure system, electrocardiogram and pulse oximetry. Patients with major cardiac histories may also be monitored with a bioimpedance cardiac output monitor. A staff anesthesiologist and resident or nurse anesthetist monitor all patients. Hemodynamic data are monitored as a baseline and then every 5 minutes throughout the phlebotomy. The phlebotomy typically requires 10 to 15 minutes but the anesthesia team may request it to be prolonged or terminated if instability occurs. Once the phlebotomy is completed or if hemodynamic problems are encountered crystalloid or colloid volume replacement is administered. After volume replacement, sitting and standing orthostatic hemodynamics are checked and the patient discharged if fully stable. 24 hours after the procedure a follow up phone call is made to make sure no symptoms have developed such as a change in angina occurrence or character.

Progress:

To date 105 phlebotomies have been conducted on 47 patients in the last 7 months of the program. At the present time 5 patients are phlebotomized per week. The program is conducted one morning a week and the maximum number of 5 patients is due to present space limitations. A larger space is being sought and plans are being developed to expand the program to 25 per week. At the present time, more patients are applying for autologous blood donation than can be cared for and a waiting list has been created. Hemodynamic data have shown significant decreases in BP (20-30%) and cardiac output (20%) without increases in heart rate (2). Three patients have had syncopal episodes, five patients have had their phlebotomy terminated due to hypotension despite fluid administration. One patient at 24 hours did have a change in his anginal symptoms and was admitted to the intensive care unit to rule out a myocardial infarction.

Discussion. Little data is available upon the risk of blood donations by patients with major cardiovascular disease because blood banks have refused to phlebotomize such patients in the past. Therefore "high-risk" patients have effectively been discriminated from the use of autologous blood transfusion programs. The training and experience of anesthesiologists focuses upon monitoring hemodynamic function, anticipating changes and providing therapy or resuscitation where necessary. Their role in providing health care outside of the operating room setting has been expanding, and includes work in pain clinics, intensive care units and emergency services. This model program adds another dimension to the role that anesthesiologists may play in patient care. The autologous donor program allows for an early preoperative interaction of the anesthesiologist and the surgical patient. Preoperative teaching and data acquisition occurs thereby benefiting patient care and increasing public visibility of the anesthesia specialty. The development and demand for growth of this program reflects patient and physician demand for autologous transfusion therapy. Generalization of such programs throughout the country could help decrease the dependency on bank blood, decrease the spread of infectious disease, increase patient understanding of anesthesia care and provide physiologic data to support the safety of phlebotomy in this group of patients. Although this model program is in its infancy, assessment of risks of phlebotomy based upon disease state will lead to development of protocols maximizing safety for high-risk patients donating autologous blood preoperatively.

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Title: THROMBOELASTOGRAPHIC DIAGNOSIS OF COAGULOPATHIES IN PATIENTS UNDERGOING CARDIOPULMONARY BYPASS

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Introduction. Thromboelastography (TEG) a whole blood viscoelastic coagulation test, has recently gained utilization intraoperatively for guiding coagulation therapy in liver transplantation and cardiopulmonary bypass (CPB) (1,2). TEG measures the interaction of protein procoagulants in the clotting cascade with the platelet surface. Clot strength is monitored from the time of initial fibrin formation through fibrin cross linking, retraction and eventual lysis. In contrast, routine coagulation profile tests and the activated clotting time (ACT) monitor coagulation only until the time of initial fibrin formation. Also, routine coagulation testing does not assess platelet function or the interaction of the platelet surface and the coagulation cascade. TEG shows good predictive accuracy (87%) for post CPB hemorrhage whereas routine coagulation profile monitoring is less than 50% accurate (2). Post CPB hemorrhage has been extensively studied and decreases in platelet activity (number and function) are the most common defects noted (3). TEG, provides clinically applicable data with more scope than present tests. No studies have reported analyzing the incidence and character of coagulopathies in CPB cases using TEG.

Methods. TEG whole blood coagulation monitoring has been added as a routine procedure performed pre and post bypass in addition to activated clotting times (ACT) at our institution. Samples for TEG testing were taken from the indwelling arterial line after withdrawing and discarding 10 or more cc's of flush solution. TEG's were run utilizing .35 cc of whole blood for at least 90 minutes. TEG tracings were analyzed for R, K, α, MA and A_{60} values. Pre and post CPB TEG parameter results were analyzed and classified as normal, hypercoagulable, hypocoagulable (platelet dysfunction) hypocoagulable (factor deficiency or residual anticoagulant) or fibrinolytic.

Results. 118 consecutive CPB cases have been monitored with matching pre and post bypass TEG data. 99 of these cases were coronary artery bypass graft (CABG) procedures, 14 were valve replacements or combined CABG and valve replacements, and 5 were either congenital cardiac or thoracic aneurysm repairs. The incidence of specific coagulopathies are shown in Table 1.

16 patients were on pre-bypass heparin within 4-8 hours pre CPB and all of these patients demonstrated hypocoagulability due to anticoagulation pre-CPB.

Discussion. The presence of coagulopathies pre-CPB was greater than post CPB, however, the characterization of those abnormalities were different. Pre CPB hypocoagulability due to factor deficiency/anticoagulation were as prevalent platelet as abnormalities were equally prevalent. After CPB, platelet abnormalities were most common.

Table 1:	Pre-CPB		Post CPB	
TEG Result	Number	Percent	Number	Percent
Normal	36	31%	65	55%
Abnormal	82	69%	53	45%
Hypocoagulable: Platelet Abnormality	34	29%	37	23%
Hypocoagulable: Factor deficiency anticoagulation	34	29%	2	2%
Hypercoagulability	5	4%	5	4%
Fibrinolysis	9	8%	9	8%
	n=118		n=118	

Pre-operative anticoagulation and drug therapy explains hypocoagulability pre CPB. Most patients were utilizing multiple drug regimens for control of cardiac dysfunction including aspirin, dipyridamole, nitrates, calcium channel blockers and beta blockers. These agents all decrease platelet activity. Patients who were hypocoagulable due to anticoagulation pre CPB after receiving protamine post CPB did not show anticoagulated tracings. However, those showing platelet hypocoagulability pre CPB did not always demonstrate that coagulopathy post CPB. Many other patients who were normal or who had other coagulopathies pre CPB demonstrated only a platelet hypocoagulability post CPB. Previous work has shown platelet function to be the most common post CPB coagulopathy and our data further supports that work (3). Fibrinolysis and hypercoagulability were also encountered, although they would not routinely be discovered without TEG monitoring. Hypercoagulability and fibrinolytic abnormalities were matched pre and post CPB in only 2 respectively. Development of in vitro protocols utilizing epsilon amino caproic acid may further characterize fibrinolytic coagulopathies in the future. More extensive investigation of the causes and incidence of hypercoagulability is necessary to assess its affect upon post CPB infarction rate and patient outcome. In summary, the future use of viscoelastic monitors in CPB will assist in guiding therapy, and provide further understanding of coagulopathies that not been routinely followed by existing coagulation monitoring.

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Title: A FIVE MINUTE WAITING PERIOD MAKES THE PRIMING DOSE EFFECTIVE

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Introduction. Conflicting reports exist concerning the effectiveness of the priming dose in shortening the time between the intubation dose and intubation (1,2). One possible cause for these conflicting results is the variation of time between the priming and the intubating doses. In the cat the suppressive effect of vecuronium on motor nerve endings reaches maximum in 5 min (3). Therefore, this study was undertaken to determine the effectiveness of a 5 min waiting period between the priming and intubating doses of vecuronium, pancuronium and atracurium.

Methods. Approval of the Institutional Review Board was secured, and informed consent was obtained from 45 patients ranging in age from 17 to 61 years, ASA physical status I and II, undergoing gynecological and orthopedic surgery. Patients with a history of a difficult intubation or on any medications affecting neuromuscular function were excluded from the study. Premedication consisted of meperidine and glycopyrrolate. Anesthesia was induced with thiopental 2-3 mg/kg, and fentanyl 2 ug/kg, maintained with 67% nitrous oxide in oxygen, and supplemented with fentanyl as needed. No potent inhalation anesthesia gases were used. The patients were randomly divided into three groups of 15, with each group receiving one of the three muscle relaxants, vecuronium, pancuronium and atracurium. The intubating dose of the muscle relaxant was divided into two fractions: the priming dose which was 1/10 of the intubating dose and administered 5 min before the intubating dose, and the second dose which contained the balance (9/10) of the intubating dose. The intubating doses were 0.1 mg/kg for vecuronium and pancuronium, and 0.5 mg/kg for atracurium. The priming doses were 0.01 mg/kg for vecuronium and pancuronium, and 0.05 mg/kg for atracurium. The balances administered for intubation were 0.09 mg/kg for vecuronium and pancuronium, and 0.45 mg/kg for atracurium. The ulnar nerve was supramaximally stimulated at the wrist. The isometric muscle contractile responses to train of four (T4) and tetanic stimulation of 50 Hz applied for 10 sec were measured, using a Professional Instruments adductor pollicis monitor (APM). The output of the APM was simultaneously displayed on the screen of a Datascope 2000A ECG and blood pressure monitor, and recorded on a penwriter. After the balance of the intubation dose, T4 stimuli were delivered continuously until the T4 train had only one contractile response. Then the ulnar nerve was stimulated at 50 Hz for 10 sec. When a complete tetanic fade developed, endotracheal intubation was undertaken. The time from the administration of the balance of the intubating dose to intubation was measured. Jaw relaxation, vocal cord relaxation and the patient's reaction to the intubation were evaluated using a scaling score of 0-4, with 4 being excellent, 3 good, 2 fair, 1 difficult, and 0 impossible (4).

Results. The continuous display of the APM output on the screen of the ECG and blood pressure monitor made the assessment of the state of neuromuscular function simple and easy. The average times (±SEM) between the intubating doses and intubation were 1.1 ± 0.05 min, 1.4 ± 0.04 min, and 1.5 ± 0.14 min for vecuronium, atracurium and pancuronium, respectively. All patients were intubated successfully and without difficulty. The average ratings (±SEM) for the intubating conditions were 3.9 ± 0.07, 3.7 ± 0.13, and 3.6 ± 0.15 respectively for vecuronium, atracurium and pancuronium.

Discussion. The continuous display of the APM output on the screen of the ECG and blood pressure monitor allowed the close examination of the true state of neuromuscular function and provided a readily available means for observing the muscle responses to relaxants. The data from this study indicate that a 5 min interval between the priming and the intubating doses produces a significant shortening of the intubating time for the three muscle relaxants. The data clearly demonstrate that when the T4 has only one contractile response and complete tetanic fade has developed, intubating conditions are excellent. In the cat, the intravenous administration of non-depolarizing muscle relaxants gives these agents sufficient time to affect prejunctional sites, thereby causing the development of tetanic fade (5). The suppressive action of vecuronium on the repetitive firing of cat motor nerve endings after high frequency conditioning is a prejunctional effect which reaches its peak in 5 min (3). In man, small doses of non-depolarizing muscle relaxants which do not affect twitch tension produce tetanic fade. The time for this effect to develop is approximately 5 min (6,7). These data strongly suggest that the prejunctional sites of action of non-depolarizing muscle relaxants have a major role in the priming principle. In summary, this study confirms that the priming principle does shorten the time between the administration of the intubating dose and intubation and that vecuronium is the most effective in this regard. Thus, in situations requiring rapid sequence induction and when succinylcholine is contraindicated, vecuronium can be the drug of choice.

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Title: CENTERLINE SYSTOLIC WALL THICKENING: A METHOD FOR QUANTITATING REGIONAL CARDIAC FUNCTION USING TRANSESOPHAGEAL ECHOCARDIOGRAPHY

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Introduction. Intraoperative transesophageal echocardiography (TEE), by virtue of its unique ability to illustrate changes in regional myocardial function (RMF) non-invasively, has become an important monitoring resource in clinical anesthesia. However, assessment of RMF using TEE remains largely a qualitative process. This poses a serious problem for incorporating TEE information in anesthesia research, since investigative work requires accurate quantitative analysis. Most methods of assessing regional myocardial function (RMF) evaluate motion of the endocardial border. However, this is heavily influenced by translational and rotational movement of the heart. Systolic wall thickening (SWT) is a sensitive indicator of contractile state of the heart. Moreover, SWT determination avoids these other motion artifacts, providing a more accurate definition of RMF. In addition, the use of a "centerline" referencing system further enhances the ability of the analysis to realistically model cardiac contraction. We present a method for measuring regional SWT from TEE images utilizing a custom-designed computer assisted centerline analysis system.

Methods. TEE data analysis is done retrospectively by reviewing video tapes, utilizing minor axis views of the left ventricle (LV) at the mid-papillary muscle level. End-diastole is determined by synchronizing images to the R wave of the ECG, and end-systole is chosen as the frame having the smallest LV cavity area. Images are digitized to a 512 X 480 pixel grid and a resolution of 256 grey levels using a video frame grabber unit interfaced with a PC 386 computer. Outlining of endocardial and epicardial edges is done by picking discrete points along these surfaces on the image using a "mouse" pointing device (Panel 1). The remaining points of the outlines are computed using a Catmull-Rom spline interpolation algorithm, and form smooth continuous edges (Panel 2). From these, an intermediate outline, the centerline, is computed as a set of 100 points equidistant from the endo- and epicardial edges (Panel 3). Wall thickness chords are then constructed as perpendiculars to tangents around the centerline, and intersect the original cardiac borders (Panel 4). Chords are numbered, beginning in each image at the posterior papillary muscle (PPM). This provides a correction for rotational movement of the heart between images. Chord lengths are stored for both end-diastolic and end-systolic frames, and are used to compute SWT (Fig 1). This is usually expressed as a percent change, and is plotted on a polar coordinate system. Since chord 1 is always over the PPM, the LV circumference can be divided into anatomic quadrants (postero-/antero- septal/lateral). All data are stored in computer files for easy integration into statistical analysis programs.

Results. Implementation of this analysis system has been straightforward and easy to teach to other users. Studies to address the effects of anesthetics on TEE have been undertaken, and representative data shown in Figure 2. SWT is plotted linearly x chord number for a patient both before and after addition of 0.5% halothane. Marked decrease in SWT occurred as a result of halothane administration, but to a significant extent only in the lateral quadrants (chord# 60-90).

Discussion. The introduction of TEE imaging in the intraoperative setting has provide a new opportunity for many valuable investigations in cardiac anesthesiology. However, no means of applying numerical analyses have been developed to provide objective treatment of TEE data. As demonstrated, this system resolves this problem by computing SWT around the LV circumference. Further work remains to be done to provide automated real-time processing in order to provide these data intraoperatively. We conclude that our technique of measuring SWT as a quantitative determination of regional myocardial function is an objective and useful means of assessing cardiac function.

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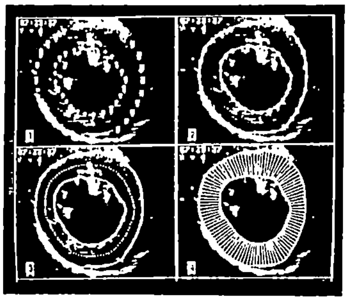
PANEL. Centerline Wall Thickening Analysis



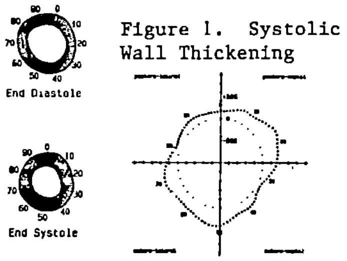
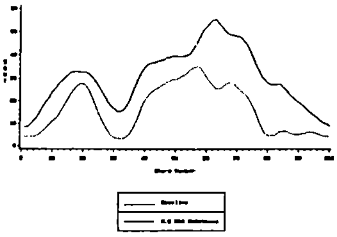


Figure 1. Systolic Wall Thickening

Fig. 2 Systolic Wall Thickening



Title: **EFFECTS OF HALOTHANE ON MECHANICAL FUNCTION OF ISOLATED MYOCARDIUM DURING HYPOXIA AND REOXYGENATION**

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Introduction. Studies have suggested that halothane (HAL) reduces the extent of myocardial damage produced by episodes of ischemia. However, it is not clear from these investigations whether this apparent protective effect of HAL is due to some specific action of the anesthetic upon myocardial tissue, or is simply the result of its improvement in the relationship of myocardial oxygen supply and demand. Models that measure the mechanical function of isolated myocardium have been used extensively to examine the direct cellular effects of various pharmacologic interventions. Studies of isometrically contracting myocardium have revealed that a period of tension prolongation occurs during reoxygenation following an episode of hypoxia. This phenomenon is known to be attenuated by certain drugs, and this information has been used to correlate its appearance with important intracellular events in myocardial ischemia.[1,2] This study examined the effect of HAL on tension prolongation during an hypoxia / reoxygenation sequence using an isolated myocardial muscle preparation.

Methods. Papillary muscles from feline hearts were suspended in an apparatus designed for mechanical studies of isometric contraction. The preparation was immersed in a bath of Krebs bicarbonate buffer superfused with 95% O_2, 5% CO_2 at 30° C. Muscle length, adjusted to attain maximal contractile strength, remained constant during the studies. The muscle was electrically stimulated at a frequency of 12 per minute and the resulting contractile force was recorded. Hypoxia was achieved by superfusing the bath with 95% N_2, 5% CO_2. HAL was added to the bath via a calibrated vaporizer. Five muscles (CTRL) underwent a 30 minute period of hypoxia (HYP) followed by immediate reoxygenation (REOX). Other muscles were subjected to the same intervention after having been exposed to 0.5% (0.5H) (n=5) or 1.0% (1.0H) (n=4) HAL for 20 minutes. HAL was continued throughout the HYP / REOX sequence, then removed after two hours of REOX. Measurements included peak developed tension (PT) (in millinewtons) and time from peak tension to 50% relaxation (t50R) (in msec). T50R is the traditional index of reoxygenation tension prolongation. Analysis of variance was used to compare results between groups, and significant difference tested at the p < .05 level.

Results. Changes in PT and t50R are shown in Figs. 1 and 2, expressed as percentages of the baseline values for that muscle (mean ± SD). HAL caused dose-related decreases in PT that were compounded by HYP; these were completely reversed by REOX and removal of HAL. T50R was significantly prolonged within 30 seconds of starting REOX in all muscles. HAL caused a trend toward diminishing this effect, but this did not reach statistical significance.

Discussion. Reoxygenation tension prolongation is thought to be the result of decreased uptake of calcium by sarcoplasmic reticula (SR) during the relaxation phase of a myocardial contraction. This may be caused by a transient dysfunction of the SR Ca^{++}-ATPase during reoxygenation. The formation of superoxide radicals (O_2^-) and the resulting lipid peroxidation are among the mechanisms thought to be responsible for this decreased calcium uptake. Drugs that attenuate the tension prolongation phenomenon can decrease O_2^- by affecting mitochondrial respiration during hypoxia[1] or by direct reduction.[2] HAL has been shown to exert similar mitochondrial effects.[3] While other drugs completely ablate tension prolongation, HAL caused only a trend toward its attenuation. This may be due to the multiplicity of intracellular effects of HAL, such as a direct inhibition of SR Ca^{++}-ATPase, resulting in offsetting actions. We conclude that HAL cannot be relied upon to attenuate the potentially deleterious tension prolongation phenomenon.

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Fig. 1. Peak Developed Tension (PT)

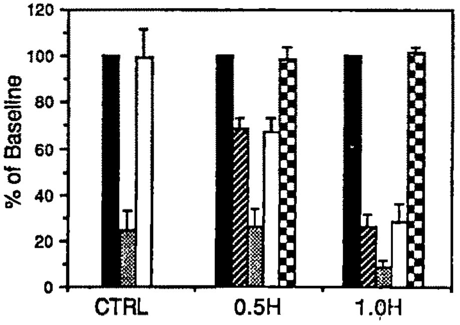
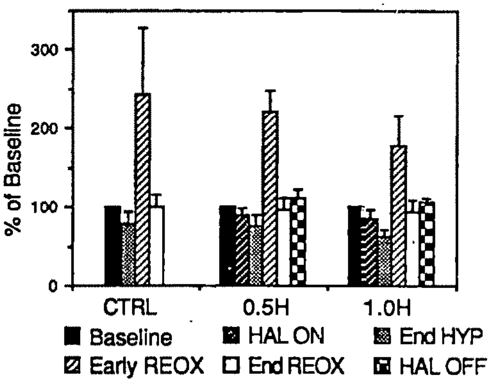


Fig. 2. Time to 50% Relaxation (t50R)



Title: PERIPHERAL VASCULAR DEPRESSION WITH SUFENTANIL IN THE DOG

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Introduction: Significant hypotension has been seen with the clinical use of sufentanil (1). Adverse hemodynamic effects with narcotics such as sufentanil have been attributed either to activation of central opioid receptors with blockade of central sympathetic outflow (2) or both opioid and nonopioid receptor-mediated peripheral vascular effects (3-4). Accordingly, we designed experiments to evaluate the action of sufentanil on the peripheral vascular system and used the canine saphenous vein as a model of adrenergically innervated vascular smooth muscle.

Methods: Following institutional approval, canine saphenous veins were obtained from mongrel dogs (20-30 kg), anesthetized with pentobarbital (30 mg/kg IV). Paired rings were mounted translumenally in jacketed organ baths containing Krebs-Ringer solution (37°C, pH 7.4, continuously aerated with 95% O_2/5% CO_2). The vessels were maintained at the optimum point of their length-tension relationship for 60 min prior to experimentation. All experiments were performed in the presence of increasing doses of sufentanil (10^{-7}-10^{-5}M) vs. vehicle-treated controls. Transmural electrical stimulation (ES) was used to contract veins via norepinephrine (NE) release from sympathetic nerve terminals. Electrical impulses (13V, 2ms, 1-10Hz, either for 10 sec or continuously) were used to contract the vein rings. Further experiments consisted of constructing dose-response curves to exogenously applied NE (10^{-9}M-10^{-4}M). Also, direct smooth muscle stimulation was performed with 40mM KCl Krebs-Ringer solution with $3X10^{-6}$M phentolamine (added to block the effect of KCl-evoked NE release). The response to sufentanil was determined when the KCl contracted rings reached a plateau (10 min). Results are expressed as percent of maximal tension ± SEM. Data was analyzed by paired t-tests and $p<0.05$ was considered significant.

Results: Response to ES was depressed by 10^{-5}M sufentanil at all frequencies examined (1Hz-44.0%, 2Hz-26.1%, 5Hz-21.5%, 10Hz-15.8% - Fig 1). Lower concentrations of sufentanil produced no significant effect on ES. Also there was significant depression of KCl evoked tension in sufentanil treated vessels (10^{-5}M) vs. controls (65±3.2% vs. 95±4.5%, see Fig 2). This effect was not seen at lower concentrations. Resting tension and the response to exogenous NE were not significantly altered by sufentanil.

Discussion: These experiments demonstrate that sufentanil significantly attenuates both ES and KCl evoked contraction. The magnitude of depression is similar; therefore, the mechanism of this effect may be direct depression of vascular smooth muscle function. This conclusion represents a previously undescribed action of a potent narcotic upon adrenergically innervated vascular smooth muscle. This effect was not observed using lower concentrations of sufentanil (10^{-7}-10^{-6}M). However, hypotension seen in patients with sufentanil may be due, at least in part to peripheral vascular actions of this drug.

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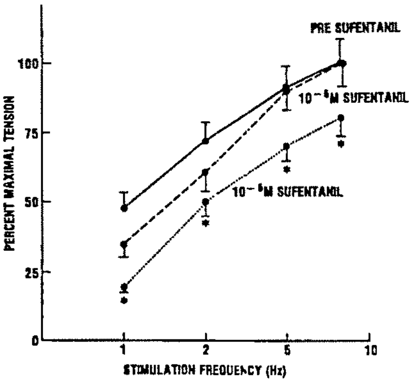
(This study was supported in part by USUHS grants C08028 and R08006.)

FIG.1

FREQUENCY RESPONSE CURVES OF THE CANINE SAPHENOUS VEIN IN THE PRESENCE OF SUFENTANIL (n = 6)



EFFECT OF SUFENTANIL ON TRANSMURAL ELECTRICAL STIMULATION OF CANINE SAPHENOUS VEINS AT DIFFERENT STIMULATION FREQUENCIES. * INDICATES SIGNIFICANTLY DIFFERENT FROM PRE SUFENTANIL (p <THAN 0.01).

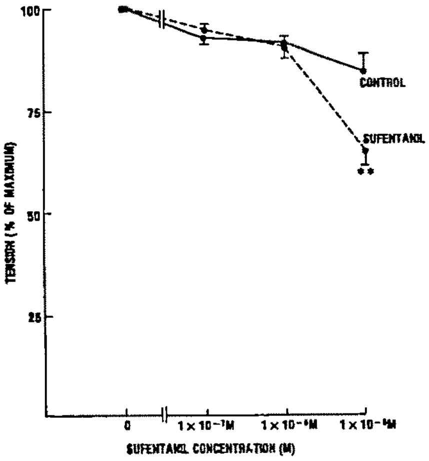


Fig 2. EFFECT OF SUFENTANIL ON 40 mM KCL INDUCED CONTRACTION.
* * INDICATES SIGNIFICANTLY DIFFERENT FROM CONTROL
(p less than 0.01, n = 6).

Title: AN ANALYSIS OF THE APPROPRIATENESS OF INTRAOPERATIVE TRANSFUSION

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Introduction: Two studies were conducted to determine the percentage of intraoperative transfusions which appeared to be indicated as evidenced by documentation in the anesthesia record, and to identify areas for educational efforts to be conducted as part of a Transfusion Medicine Academic Award program.

Methods: Criteria defining appropriate indications for administration of red blood cells (RBC), fresh frozen plasma (FFP) and platelets (PLTs) were established (Table 1-3). Transfusion was considered indicated if at least one criterion was present in the anesthesia record. No attempt was made to determine whether the number of units of blood components transfused was appropriate; only the apparent indications for initiating a transfusion incident (TI) were considered. In the first study, the anesthesia records of all patients undergoing non-cardiac surgery during a one year period were reviewed. The second study consisted of a review of the records for procedures performed during the first 3 months of 3 consecutive years. Members of the anesthesia staff were not aware of the audit criteria or the studies.

Results: There were 627 TIs in the first study (Table 4). In 26% of the TIs, established criteria were not met. The trend over the 3 years was toward more appropriate transfusion practice (Table 5), but in 22% of the 410 TIs an apparently inappropriate transfusion was administered.

Discussion: The criteria for FFP and PLT administration were based on the guidelines developed by the NIH Consensus Conferences on FFP[1] and PLTs[2]. The arbitrary Hct of 30% for RBC transfusion conforms to common practice,[3] but is not based on sound scientific data. While the estimated blood loss (EBL) is highly subjective, it is one of the clinical criteria used in determining indications for transfusion. It is probable that some of the apparently inappropriate TIs were justified. However, this cannot be determined in the absence of documentation. Despite the potential for transfusion-transmitted disease, alloimmunization and transfusion reactions, approximately one-fourth of the transfusions were administered without apparent indication. This is similar to previous reports[4,5] in which 18%-25% of RBC transfusions in surgical patients were unnecessary.

It is recommended that observations and laboratory studies (e.g. EBL, oozing indicative of coagulopathy, Hcts, coagulation studies) prompting transfusion be documented in the anesthesia record. The benefits are twofold: 1) the anesthesiologist is forced to consider the rationale for the transfusion, and 2) there is documentation in the chart, a legal record, of the justification for the therapeutic intervention. It is further recomended that educational efforts be directed toward promoting appropriate transfusion practices.

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Table 1: Criteria for RBC Administration*

Preoperative Hct < 30%
Intraoperative Hct < 30%
Estimated blood loss > 15% EBV+

Table 2: Criteria for FFP Administration*

PT > 1.5 X normal (> 17 secs)
aPTT > 1.5 X normal (> 47 secs)
RBC transfusion > 1 EBV+

Table 3: Criteria for Platelet Administration*

Platelet count < 50,000/ul
RBC transfusion > 1 EBV+
Bleeding time > 2 X normal (> 15 mins)

*Presence of one criterion = indication for transfusion.

+Estimated blood volume, calculated as 70 ml/kg

Table 4:

N	Component	Indicated
520	RBC	420 (81%)
79	FFP	24 (31%)
28	PLT	18 (64%)

Table 5

Year	N	Component	Indicated
I	120	RBC	89 (74%)
II	108	RBC	89 (82%)
III	124	RBC	120 (97%)
I	24	FFP	7 (29%)
II	11	FFP	1 (10%)
III	12	FFP	8 (67%)
I	6	PLT	4 (67%)
II	3	PLT	3 (100%)
III	2	PLT	2 (100%)

This research was supported in part by Transfusion Medicine Academic Award (K07-HL1257) from the National Heart Lung and Blood Institute, National Institutes of Health.

Title: pH Adjustment of 2-Chloroprocaine Quickens the Onset of Epidural Anesthesia
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Introduction: Increasing the pH of solutions of lidocaine (1) and bupivacaine (2) has been shown to quicken the onset of epidural anesthesia (EA). Recently, a study of pH-adjustment of 3% 2-chloroprocaine (2-CP, Nesacaine CE^R) found no significant change in the onset of EA (3). Since then, a new bisulfite-free solution of 2-CP (Nesacaine MPF^R) has become available. Therefore we performed a randomized, double blind study to determine if and to what extent pH adjustment of Nesacaine MPF^R affects the onset and duration of EA.

Methods: 40 ASA class I and II patients scheduled for lower extremity surgery under EA (ages 18-55) were randomly divided into two equal groups, after obtaining institutional approval and written informed consent. Group I received 15 ml of pH-adjusted 3% 2-CP (pH adjusted) and Group II received 15 ml of unadjusted 3% 2-CP (plain). The solutions were freshly prepared in the following manner: for Group I, a 30 ml vial of Nesacaine MPF^R (Astra) was opened, 3 ml of local anesthetic was withdrawn, and replaced with 3 mEq $NaHCO_3$. For Group II the process was the same, except that 3ml of 0.9% NaCl was added instead of $NaHCO_3$. Epinephrine (1:200,000) was freshly added to both solutions. The final concentration of 2-CP was 2.7% in both solutions.

The patient was positioned in the lateral decubitus position (operative side dependent). The epidural space was identified at L 3/4 by loss of resistance using a Tuohy needle. A 3 ml test dose of the local anesthetic (LA) solution was injected and if no heart rate increase was observed a further 12ml (total volume 15ml) were incrementally injected over 2 minutes. A catheter was then inserted 3-5 cm into the epidural space, taped, and the patient turned supine. Time "zero" was the end of LA injection. Using a safety pin as a testing device, the times were recorded as follows: 1. Analgesia of anterior thigh (L_2 dermatome): when the patient could no longer discern sharp from dull sensations, 2. Anesthesia at L_2: when the patient felt no sensation when touched by the safety pin, 3. Time to maximum level of hypesthesia: when the sharpness of the pin felt the same as when touched at the shoulder, 4. Time to 2-segment regression of hypesthesia, and 5. Maximum level of hypesthesia. pH of the LA solutions was measured with a Corning^R pH Meter 125. Data was tested for statistical significance using a 2-tailed unpaired t-test. Significance was assumed at $p<0.05$. Data are reported as Means ± S.D.

Results. All patients developed satisfactory EA. There were no statistically significant differences between the two groups in age, height, or weight. The pH of unaltered 2-CP was 3.25. The pH of the plain 2-CP (saline and epinephrine added) and of the pH adjusted 2-CP were 3.26 and 7.28, respectively. Times to reach analgesia, anesthesia, and maximum level (of hypesthesia) were significantly shorter in Group I compared to Group II. Maximum level and time to 2-segment regression were not statistically different between the groups (see table).

Discussion. Our study demonstrates that raising the pH of 3% 2-CP (Nesacaine MPF^R) from 3.25 to 7.28 quickens the onset of analgesia and anesthesia at the L2 dermatome by an average of 2.5 and 6.6 minutes respectively, which is both statistically and clinically significant. In a busy anesthesia practice operating room turn over time could be therefore improved by adjusting the pH of 3% 2-CP for EA.

A previous study found no effect of raising the pH of 3% 2-CP (Nesacaine CE^R) to 7.08 on onset times of anesthesia (3). Several explanations are possible: The amount of $NaHCO_3$ added, the use of post-partum vs non-pregnant subjects (4), and different preservatives used in Nesacaine CE (bisulfite) and Nescaine MPF (EDTA). On the basis of our results, we recommend the use of pH-adjusted 3% 2-CP to quicken the onset of EA.

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Table Anesthetic Variables in Minutes (Mean Values ± SD)

	Control Group	pH Adjusted Group	p Value
Time to Analgesia at L_2	8.8 ± 2.9	6.3 ± 1.8 +	0.0025
Time to Anesthesia at L_2	19.0 ± 6.1	12.4 ± 5.1 +	0.0006
Maximum Level of Hypesthesia) (Thoracic Dermatome)	8.8 ± 1.7	8.0 ± 1.6	0.13 (ns)
Time to Reach Maximum Level	10.4 ± 4.2	7.6 ± 2.5 +	0.014
Time to 2-Segment Regression	61.3 ± 3.1	65.2 ± 10.5	

+ = Statistically significant differences at $p<0.05$

TITLE: THERMOREGULATORY THRESHOLD IS INVERSELY PROPORTIONAL TO ISOFLURANE CONCENTRATION

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Introduction. Intraoperative thermoregulatory vasoconstriction occurs at ≈ 34.5°C during halothane/oxygen and nitrous oxide/fentanyl anesthesia.[1,2] Because physiological responses to anesthesia (*e.g.*, myocardial depression) are usually dose-related, we tested the hypothesis that thermoregulatory inhibition is correlated with isoflurane concentration.

Methods. With approval from our Institutional Review Board and written consent, we studied six healthy, unpremedicated patients electively donating a kidney. Anesthesia was induced and maintained with isoflurane/oxygen and vecuronium. Patients were randomly assigned to receive "high-dose" isoflurane (to maintain systolic blood pressure 110-120 mmHg) or "low-dose" isoflurane (to maintain diastolic blood pressure 85-90 mmHg). End-tidal isoflurane concentrations were determined using a mass spectrometer. Hypothermia was induced by administration of 5-7 L lactated Ringer's solution cooled to 4°C. We measured temperatures of the tympanic membrane, forearm, and fingertip at 10-min intervals throughout surgery. Thermoregulatory vasoconstriction was prospectively defined as a skin-surface temperature gradient (forearm — fingertip) ≥ 4°C.[1,2] The thermoregulatory threshold was defined as the tympanic membrane temperature at which vasoconstriction occurred. Following vasoconstriction, patients were rewarmed using all appropriate techniques. The thermoregulatory threshold also was determined in one unanesthetized volunteer.

Results. The thermoregulatory threshold and end-tidal isoflurane concentration were inversely proportional (figure). All subjects vasoconstricted except the first patient who was given the highest isoflurane concentration (2.2%).

Discussion. Our data confirm that the thermoregulatory threshold during isoflurane anesthesia is a strong function of end-tidal concentration. Dose-dependent inhibition of central thermoregulation is consistent with progressive isoflurane-induced suppression of cerebral function.[3] Isoflurane dilates arterioles but causes little direct inhibition of cutaneous, thermoregulatory vasoconstriction. Thus, the patients in this study developed skin-temperature gradients similar to those observed previously in unanesthetized volunteers, indicating that the intensity of vasoconstriction was preserved although isoflurane diminished the threshold.[4] Although, hypothermia decreases MAC ≈ 5%/°C, this relatively modest increase in anesthetic potency is insufficient to explain the substantial thermoregulatory inhibition we observed. Thermoregulatory vasoconstriction significantly decreases heat loss to the environment, typically preventing further hypothermia.[1,2] The patient given 2.2% isoflurane did not vasoconstrict and thus rapidly became more hypothermic than intended. Although this patient reached a core temperature of 31°C before rewarming, extending the regression line to 2.2% isoflurane suggests that vasoconstriction would not be expected until nearly 30°C. In summary, the thermoregulatory threshold for cutaneous vasoconstriction in humans decreases ≈ 3°C/% isoflurane.

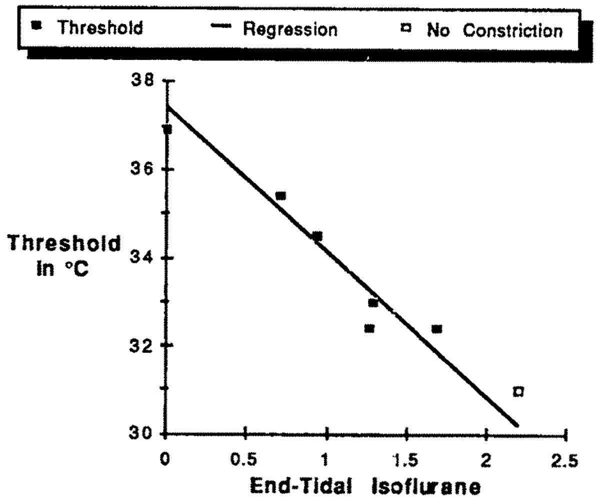

Figure. The thermoregulatory threshold plotted against end-tidal isoflurane concentration. The dark line is the least-squares regression calculated using only the subjects who vasoconstricted: **Threshold = -2.9*[isoflurane] + 37, r=-0.96.**

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Title : AUTONOMIC HYPERREFLEXIA IN SPINAL CORD INJURY PATIENTS DURING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

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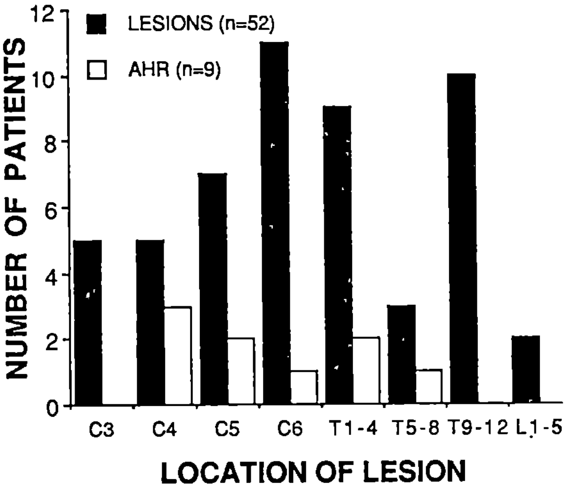
Introduction. Extracorporeal shock wave lithotripsy (ESWL) is widely used as an alternative to percutaneous nephrolithotomy and surgical removal of stones. General or regional anesthesia is generally required for patient comfort and immobility. Patients with high spinal cord injuries are left with motor and sensory loss below the level of the lesion and so do not require anesthesia for control of pain or body movement. However, distention and instrumentation of a hollow viscus during cystoscopy and urological surgery are well known to elicit reflex sympathetic vasoconstriction below the level of the lesion. The resulting hypertension triggers a centrally mediated reflex bradycardia and vasodilatation above the lesion, but vasoconstriction below the lesion remains unopposed. The occurrence of this disorder, autonomic hyperreflexia (AHR), has not been reported during ESWL. Our aim was to assess if AHR occurs during ESWL in spinal cord injured patients and if they would benefit from anesthesia to avoid AHR during ESWL.

Methods. The hospital records of all patients at our institution treated for urinary tract stones by ESWL over two years were examined retrospectively. Each patient received at least 500 cc of i.v. saline before anesthesia and each patient was monitored non-invasively for blood pressure, EKG and oxygen saturation. All spinal anesthetics were administered using standard techniques at $L_{3, 4}$ or $_5$. Of those patients with high spinal lesions receiving intrathecal local anesthetics, the adequacy of block was assumed by a free flow of clear CSF with a positive aspiration test after injection of the anesthetic.

Results. 1,647 adult (1,232 male; 415 female) patients (53 ± 3 SEM yr; ASA I-III) presented for ESWL. 124 (8%) had general anesthesia, 646 (39%) had epidural anesthesia, and 877 (53%) had spinal anesthesia. Of these patients, 52 (all male, 48 ± 2 yrs) were identified to have non-recent, complete spinal cord lesions at locations shown (fig). Of the 52 patients, 7 (3 with lesions at C_3 and 4 others with lesions at C_5, T_7, T_9 and T_{12}) had general anesthesia; the remainder had spinal anesthesia for ESWL. Of the 22 patients who had cervical lesions and had spinal anesthesia for ESWL, 6 were found to have experienced AHR (figure), a significant incidence of P<.01; 6 of a total of 9 who developed AHR had no prior history of AHR. Maximal and minimal blood pressure and heart rate changes were:

	BP (sys/dia mmHg)	Heart Rate (b/min)
Pre-spinal	120+ 3 /72 + 5(SEM)	73 + 7(SEM)
Post spinal	96∓9 /58 ∓ 4	82 ∓ 7
AHR	198∓11 /112∓ 6	53 ∓ 8

In 4 patients hemodynamic changes were associated with complaints of chest pain, flank pain and headache. In 1 patient AHR occurred during ESWL 60 min after intrathecal injection of 15 mg of 0.75% bupivacaine; 6 patients who received 5% lidocaine with 5 ug/ml epinephrine had AHR during ESWL 90, 95 and 95 min after 100 mg lidocaine; 45 min after 80 mg lidocaine; 75 min after 50 mg lidocaine; and 20 min after 50 mg lidocaine. In the 2 remaining patients, AHR occurred 85 min after 280 mg epidural lidocaine (2%) and 20 min after light general anesthesia. Hypertension, which lasted about 15 min, was treated with hydralazine, labetalol, procardia, and nitroglycerin. Bradycardia was treated with atropine. BP and heart rate returned to pre-AHR levels with cessation of ESWL. Of the 28 patients with cervical cord lesions, 6 did not experience AHR although they had a history of AHR. Four received 12-14 mg of tetracaine (1%) and ESWL ended 40, 60, 90 and 150 min after spinal anesthesia. Two others received 75 and 100 mg lidocaine and ESWL ended 70 and 80 min after spinal anesthesia.



Discussion. AHR occurs at least once in about 85% of patients[1] with spinal cord injuries above T_6 and is commonly triggered by urologic procedures.[2] Our study shows a significant incidence (6 of 28) of AHR in patients with cervical cord lesions during ESWL despite spinal anesthesia. But none of the patients with high cervical injuries who had undergone general anesthesa, nor other patients who had spinal anesthesia with higher doses of local anesthetics and shorter ESWL procedures, developed AHR. A review of our experience with ESWL and spinal cord injured patients indicates that ESWL can trigger AHR in a significant number of patients. Because all patients received anesthesia for ESWL, we could not precisely evaluate the effectiveness of general vs. regional anesthesia in preventing AHR. However, it appears that general anesthesia protects well against AHR in patients with cervical cord lesions and that an adequate level of regional anesthesia as well as a shorter duration of ESWL may help to avoid development of autonomic hyperreflexia.

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Title: KETAMINE INFUSION: AN ALTERNATIVE ANESTHETIC TECHNIQUE IN THE MORBIDLY OBESE PATIENT

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Introduction. Morbidly obese patients are at significant risk for cardiopulmonary complications following major intraabdominal surgery (1). Ketamine anesthesia has several potential advantages in this group of patients, to include minimal respiratory depression, (2) improved pulmonary compliance (3) and indirect cardiostimulatory effects (4). We describe a technique using ketamine by continuous infusion as the primary anesthetic in a group of morbidly obese patients undergoing vertical banding gastroplasty.

Methods. After receiving approval from our Human Investigation Committee twenty-four patients undergoing vertical banding gastroplasty for morbid obesity received ketamine 1 mg/kg, curare 3 mg, diazepan 10 mg, and succinylcholine 1.5 mg/kg (based on ideal body weight) for rapid sequence induction of anesthesia. Anesthesia was maintained with ketamine 20-60 ug/kg/min by continuous infusion, combined with 50-70% nitrous oxide and atracurium for muscle relaxation. Arterial blood gases were obtained preoperatively, 30 minutes post-induction and 30 minutes postoperatively. Heart rate and mean arterial pressure were recorded preinduction, at induction and five minutes post-induction. At the end of surgery, time to eye opening and extubation were recorded. All patients were monitored in the ICU for 24 hours and then discharged to the ward. Patients were then interviewed at 24 hours for any anesthetic complication.

Results. Ketamine with 50-70% nitrous oxide was the sole anesthetic in 19 of 24 patients. The other five required supplementation with a potent inhalational agent, and four of those five required hydralazine to control hypertension.

All patients were extubated at the end of surgery within five minutes of the last skin staple. Arterial blood gas values were not significantly different postoperatively compared to preoperative values. No patient hypoventilated postoperatively and there were no cardiopulmonary complications noted on review of discharge note. One patient described a significant emergent reaction (4%).

Mean arterial pressure increased 25% at induction, but stabilized to 10% over baseline by five minutes. Heart rate also increased 20% at induction and then stabilized at 11% over baseline.

Discussion. This study demonstrates that ketamine by continuous infusion with nitrous oxide and muscle relaxation is a reasonable and safe alternative anesthetic technique in the morbidly obese patient undergoing major intraabdominal surgery.

Narcotics are potent respiratory depressants, and potent inhalational agents undergo increased biotransformation (5) in obese patients. In addition they are myocardial depressants, respiratory depressants and have increased storage in adipose tissue which prolongs excretion. Regional anesthesia is often technically difficult in these patients. Ketamine avoids the above problems as demonstrated in this study.

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TITLE: **TIME, TEMPERATURE AND BRAIN BLOOD FLOW DURING HYPOTHERMIC CARDIOPULMONARY BYPASS**

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Introduction. Cerebral blood flow (CBF), as measured by 133 xenon (Xe) clearance, decreases with time during hypothermic cardiopulmonary bypass (CPB) (1,2). The etiology of this decline has not been fully documented nor have time-related decrements been reported in all studies (3). Temperature is a principle factor affecting CBF during CPB but its effects have not been systematically studied in humans in the absence of other conflicting influences (4). The time effect, best documented using ^{133}Xe clearance techniques (1) requires confirmation using alternative methods of measurement. We report our experience using Transcranial Doppler Sonography (TCD) to measure blood velocity continuously in the middle cerebral artery (MCA) during CPB.

Methods. Following approval by the Clinical Research Practices Committee, 5 consenting patients undergoing elective cardiac surgery were admitted to the study. After premedication with lorazepam po and morphine im, fentanyl 75 ug/kg was used for narcosis, while pancuronium 0.1 mg/kg facilitated endotracheal intubation. Mean flow velocity (FV) in cm/sec was measured in the MCA with a Carolina Medical Electronics TCD-64b applied over the temporal area. FV was monitored continuously but analyzed for statistical purposes at 10 min intervals from the onset of CPB until normothermic CPB following rewarming. During CPB, PaCO2, mean arterial pressure (MAP), pump flow (Q), and Hematocrit (Hct) were managed as is customary at our institution. A paired two-tailed t-test was used for statistical comparisons (significance = $p<0.05$).

Results. The table displays PaCO2, MAP, Q and Hct during the study. FV decreased to 80% of the initial value by the time of aortic cross-clamp and to 56% by 40 min post cross-clamp ($p>.01$) (Figure). The greatest change in FV took place during the initial cooling phase and between 10 and 20 min post-clamp, although FV continued to fall throughout the CPB period. FV increased progressively during the rewarming period, eventually exceeding the initial value by 30%.

Discussion. These results, using Transcranial Doppler Sonography as a continuous monitor of blood flow velocity, agree with previous studies reporting a decline in CBF using the 133 Xe clearance method (1-2). This change is greatest in the first 30 min of CPB, but continues throughout the CPB period. Possible mechanisms include differential cooling rates for the brain or a progressive decline in CBF related to the duration of nonpulsatile perfusion. Although the brain is highly vascular, there are wide gradients in flow and metabolism for adjacent tissues. Further, the CSF-filled ventricles of the brain cool via diffusion, a slow process. Although Murkin et al. (3) reported no time-related changes in flow in patients undergoing valvular surgery, their first CBF determination was initiated approximately 20 min into CPB, by which time much of the decrease in CBF would have already occurred. Other CBF studies (1,2) performed on CABG patients were initiated only 5 min following the aortic cross-clamp. We conclude that there is a marked time-related decline in cerebral perfusion during hypothermic, nonpulsatile CPB which must be considered when reporting on CBF. The mechanism of this decline requires investigation.

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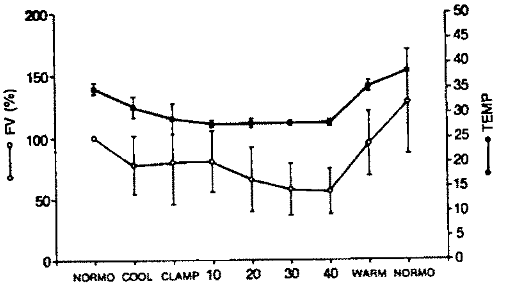
Table (means ± SD)

	PaCO2* (mmHg)	MAP (mmHg)	Q (L/min/m^2)	Hct (Vol %)
Normo	38 ± 3.6	73 ± 16	NA NA	30 ± 7
Cool	39 ± 1.8	60 ± 9	2.4 ± 0.4	21 ± 11
Clamp	39 ± 1.8	62 ± 5	2.1 ± 0.7	24 ± 8
10	39 ± 1.8	66 ± 13	1.9 ± 0.6	23 ± 4
20	39 ± 1.7	67 ± 8	1.8 ± 0.2	22 ± 5
30	40 ± 3.1	60 ± 11	2.1 ± 0.6	21 ± 6
40	40 ± 3.1	62 ± 7	2.0 ± 0.3	22 ± 5
Warm	38 ± 5.6	63 ± 7	2.6 ± 0.2	22 ± 4
Normo	38 ± 3.1	68 ± 11	3.0 ± 0.3	24 ± 4

*uncorrected for body temperature
All values are expressed as mean ± Standard Deviation (SD)



Title: POST-OPERATIVE ARTERIAL OXYGEN SATURATION — UP IN A PUFF OF SMOKE?

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Introduction. It is well known that cigarette smoke can have a profound effect on the cardiovascular and respiratory systems, and that patients who smoke cigarettes carry an increased risk of perioperative complications.[1]

A frequent complication which has been observed in otherwise healthy patients is an arterial oxygen desaturation during transport of the patient from the operating room (OR) to the post anesthetic recovery unit (PARU).[2,3]

The respiratory effects of smoking, such as increased carboxyhemoglobin levels and decreased lung function, suggest a potential for impaired postoperative oxygen saturation in patients who smoke. This study, therefore, was designed to examine the potential contribution of cigarette smoking to arterial oxygen desaturation following general anesthesia.

Methods. Informed consent and approval from our Institutional Review Board was obtained. The study population consisted of 43 ASA Class I - III adult patients who were free of respiratory disease and who underwent a number of elective gynecological and lower abdominal procedures. Information regarding smoking habits and past medical history was solicited from each patient in interviews prior to surgery. Patients were assigned to a smoking group (n=19) or a non-smoking group (n=24) based on positive current histories. Arterial oxygen saturation (SaO_2) was measured before induction of anesthesia while the patient was breathing room air using a Nelcor N-100 pulse oximeter. All patients received general anesthesia and all were intubated. Details of any preoperative medication, narcotic use, and muscle relaxant use were recorded. Adequacy of muscle relaxant reversal was tested clinically and by peripheral nerve stimulator. At the end of surgery, prior to transport to PARU, measurements of SaO_2 were taken during 100% oxygen administration; no supplemental O_2 was given en route to PARU. In addition, end-tidal CO_2 ($ETCO_2$), end-tidal agent concentration (ETAg), and end-tidal N_2O (ETN_2O) concentrations were measured using an Anesthesia Circuit Evaluator (Traverse Medical). These measurements were furthered repeated on arrival in the PARU. Transport times, patient temperatures, and respiratory rates were recorded and the patient's level of consciousness was scored using a standard recovery scale.

Observers were blind to the patients' smoking habits. Analysis of categorical variables was performed by chi-square analysis and analysis of variance for continuous variables. Unless stated to be otherwise, significance was established at a level of five percent.

Results. The smoking and the non-smoking groups were comparable with respect to sex, type of procedure, duration of anesthesia, and duration of surgery. The non-smoking groups were significantly older than the smoking group, however (mean ages 48.4 ± S.D. 20.8 *vs.* 37.0 ± 9.9 years). There were no differences between the two groups in terms of the use of preoperative medications, anesthetic agents, narcotics, or muscle relaxants. There were no differences in the respiratory rates, temperatures, or levels of consciousness between the smokers and the non-smokers. The two groups were also comparable with respect to OR and PARU ETAg's and ETN_2O's. There were no statistical differences between OR and PARU $ETCO_2$ levels (41.9 ± 11.4 *vs.* 40.6 ± 7.8), nor were there any differences in these values between smokers and non-smokers. SaO_2 levels, however, dropped significantly during transport, a drop which was exacerbated in the smoking group (Table 1). Pack years ranged from 7 to 55 years (mean 15.3 years). Three patients in the smoker group had PARU SaO_2 levels of less than 85%, compared to none in the non-smoker group, a difference which was statistically significant.

Discussion. It is well known that the incidence of perioperative complications is increased in persons with respiratory disease and/or in patients who smoke heavily. Some of the more important consequences of smoking with respect to the administration of anesthesia include a decrease in functional residual capacity (FRC) and an increase in airway closing capacity (CC). Patients who smoke heavily or who have chronic obstructive lung disease or who are obese may, during anesthesia, have closing capacities which approach or exceed the FRC, resulting in ventilation perfusion mismatching, atelectasis, and arterial desaturation. Smoking also increases the levels of carboxyhemoglobin (COHb) in the blood which results in a decrease in the amount of Hemoglobin (Hb) available for combination with oxygen and, thus, a decrease in oxygen content and a shift of the O_2 dissociation curve to the left.[1]

That SaO_2 levels drop significantly during transport is well known,[2,3] however, that this may occur to a greater extent in smokers should alert the anesthesiologist to the need for supplemental O_2 access during transport and in the immediate post-operative period in this patient population. Although statistically significant the 3.4% difference in mean PARU SaO_2 levels between smokers and non-smokers is not clinically important. That the incidence of PARU SaO_2 levels below 85% was significantly higher among smokers should, however, be cause for concern. In fact, the SaO_2 levels in smokers may have been even lower than stated, as pulse oximetry has been shown to over represent SaO_2 in the presence of COHb,[4] although the degree of any overestimation would probably be minimal at the levels of COHb routinely found in smokers. Further studies measuring COHb levels are underway. Although the use of preoperative medications and narcotics in the population could have contributed to decreased SaO_2 levels due to respiratory depression, and thus decreased SaO_2 levels, that the postoperative respiratory rates and the use of narcotics and premedicants were similar in the two groups decreases their chance of confounding.

In conclusion, this study shows that postoperative arterial desaturation may be exacerbated in patients who smoke, independent of CO_2 retention or lack thereof, and that in the absence of a pulse oximeter these patients may require supplemental oxygen during transport or upon arrival in PARU.

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Table 1.

SaO^2 (mean ±S.D.)

Group	Induction	OR	PARU
Non-smoker (n=23)	96.2 ± 2.1	99.4 ± 0.9	94.0 ± 3.7*
Smoker (n=18)	96.7 ± 2.1	98.8 ± 1.8	90.6 ± 6.6*†

* $p<0.01$ PARU *vs.* OR
† $p<0.05$ PARU *vs.* non-smokers

Title: **THE INTERACTION BETWEEN SEVOFLURANE AND SODA LIME OR BARALYME®**

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Introduction.

Sevoflurane is a new inhaled anesthetic with 1) a small blood/gas partition coefficient, and 2) an associated rapid induction of and recovery from anesthesia. However, soda lime degrades sevoflurane, and this has limited the developement of sevoflurane. In the present study, we have investigated whether silica, a component of soda lime, causes absorption and/or degradation of sevoflurane. In addition we have studied whether Baralyme®, which does not contain silica, causes the same degradation of sevoflurane as does soda lime.

Methods.

Experiment 1: Eight sets of five 600ml cylindrical glass containers with openings at each end were prepared. Each set was filled with 0, 0.1, 1, 10, 20, 50, or 100% silica with the balance being sodium hydroxide. A flow of 41/min 2% sevoflurane in 100% oxygen was passed through each container for 30 seconds at room temperature.

Experiment 2: The glass containers were filled with soda lime, and 2.0% sevoflurane, 2.0% enflurane, 1.5% isoflurane, 1.0% halothane, or 50% nitrous oxide was passed through each container for 3 minutes at room temperature. This was repeated with Baralyme® in place of soda lime. Anesthetic concentrations of inflow gas and outflow gas were measured with a Parkin-Elmer 1100 mass spectrometer. Recovery was calculated by mass balance.

Experiment 3: Baralyme®, 100g, was placed in each of eight 580 ml flasks, the flasks sealed with a Teflon® stopper, and each flask placed in a water bath at 80°C. 100ml of I-653(1.1%), sevoflurane(0.4%), isoflurane(0.4%), and halothane(0.5%) were introduced concurrently and the concentration of each anesthetic measured by gas chromatography over the next several hours.

Results.

Experiment 1: 100% of sevoflurane was recovered after administration of 2.0% sevoflurane for 30 seconds through sodium hydroxide without silica. However, no sevoflurane was recovered from 100% silica. Recovery was 97% from the mixture containing 0.1% silica (the same ratio as in soda lime), and nil from mixtures containing more than 50% silica.

Experiment 2: 97.1±0.3% (mean±SEM) of sevoflurane passed through soda lime for 3 minutes was recovered. 100% recovery occurred with the other anesthetics. However, after passing through Baralyme®, 100% recovery occurred with all the anesthetics, including sevoflurane.

Experiment 3: Sevoflurane was rapidly destroyed by Baralyme® at 80°C (99.999±0.001% per hour). The rate of destruction of the other anesthetics was considerably lower: 1.6±0.2% I-653; 10.3±0.7% isoflurane; and 28.7±0.4% halothane per hour.

Discussion.

The results from this study suggest that sevoflurane is absorbed by silica, a component of soda lime. This absorption may be an important factor limiting the rate at which induction of anesthesia may be achieved in a circle absorption system with sevoflurane. For this, Baralyme® may be a better choice than soda lime for administration of sevoflurane.

Although Baralyme® does not appear to absorb appreciable quantities of sevoflurane, like soda lime, Baralyme® can degrade sevoflurane. At the high temperature used in this test, the rate of degradation (about 90% for each 10 minute period) exceeded by 5-fold that found previously with soda lime at the same temperature (1). This constitutes a possible disadvantage to the use of Baralyme® as a replacement for soda lime in the clinical administration of sevoflurane.

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Title: **HALOGENATION AND ANESTHETIC POTENCY**

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Introduction. Structure-activity relationships may provide insights into the mechanisms by which anesthetics act. Previous studies have shown that the potency of organic compounds increases as a given halogen is replaced with successively larger halogens (1,2). However, these studies often are limited in the accuracy of determination of potency, rarely correlate potency with physical properties, and usually fail to include ether compounds. Because establishing relationships between structure and activity may shed light on anesthetic action, we studied the new anesthetic, I-537 (CF_2H-O-CBrH-CF_3), relative to two other ether anesthetics, I-653 (CF_2H-O-CFH-CF_3) and isoflurane (CF_2H-O-CClH-CF_3), for which MAC and oil/gas partition coefficients are accurately known.

Methods. We determined olive oil/gas (N=6) and blood/gas (N=4) partition coefficients by standard techniques (3,4). Blood was obtained from fasting, presurgical patients after informed consent and approval by our Research Committee. MAC was determined in 8 Sprague-Dawley rats by a modification of standard techniques (5). Because of the relatively high blood solubility of I-537 (see below), in order to assure approximate equilibration between inspired gas (which we measured) and alveolar gas, we applied a supermaximal stimulus to the tail at step-wise *decrements* in concentrations, beginning with a concentration that exceeded MAC by two or more steps. The process was repeated once (i.e., MAC was determined twice in each rat). The duration of anesthesia prior to reaching the first concentration permitting movement was 140 min.

Results. The blood/gas and oil/gas partition coefficients of I-537 were 3.22±0.10(means±SD) and 245±6, respectively. The MAC was 0.52±0.07%.

Discussion. Anesthetic potency increases 4.1-fold when chlorine (isoflurane) replaces fluorine (I-653); and 2.7-fold when bromine (I-537) replaces chlorine. Our results in this ether series confirm both qualitatively and quantitatively those for several series of alkanes (1,2). Combined, such findings indicate that anesthetic potency increases consistently with increasing molecular weight. This effect of increasing weight (and/or change in associated physical properties) may be applicable to the design of new anesthetics.

The increase in potency due to halogen substitution correlated closely with increased lipid solubility (Table). The mean of the product of MAC and the oil/gas partition coefficients for I-653, isoflurane, and I-537 was 118±10. However, this value is significantly less than the mean of the values obtained in other studies for methoxyflurane, halothane, fluroxene, and cyclopropane (238±26) (6,7). Because methoxyflurane and fluroxene are ethers, the difference in product is not simply a consequence of the ether structure. This difference suggests that olive oil is not precisely representative of the anesthetic site of action. The reason for this difference is not apparent, but may provide a clue to the character of the site of anesthetic action.

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Table.

	CF_2H-O-CXH-CF_3		
X	MAC (%ata)	O/G	MAC x O/G
F	5.72	18.7	107
Cl	1.38	90.8	120
Br	0.52	245	127

O/G: olive oil/gas partition coefficient at 37°C.

Title: COMPUTERIZED EEG MONITORING AND SELECTIVE SHUNTING: CORRELATION BETWEEN ISCHEMIC EEG TIME AND OUTCOME

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Introduction: The reliability of selective shunting based on computerized EEG (CEEG) monitoring has not been addressed. Rampil et al (1) employed a 50% reduction of the spectral edge frequency (SEF) to identify cerebral ischemia during 111 (>95% shunted) carotid endarterectomies (CEA). They found a correlation between isolated ischemic EEG events of $\geq$ 10 min and the occurrence of new postoperative neurological deficits, but only in patients without a prior history of cerebral infarction (CVA). Our study was designed to investigate if monitoring both the 2 channel unprocessed EEG and SEF simultaneously could be combined successfully to determine the indication for bypass shunt, and to predict postoperative neurological outcome in all patients.

Methods: Approval of our institution's Human Studies Committee was obtained. 103 consenting patients undergoing CEA were studied. 35 of these patients had a prior history of CVA. Following induction with either thiopental 4 mg/kg or etomidate 0.3 mg/kg, a stable depth of anesthesia was maintained at normocarbia with 50-70% N_2O-O_2, 0.1-0.3% end-tidal isoflurane, fentanyl 1-3 ug/kg/hr, and vecuronium. Prior to induction and throughout surgery a CEEG monitor (Interspec®-Neurotrac®) with compressed spectral array (CSA) capability was employed. This displays 2 channels (left and right cerebral hemispheres) of EEG and CSA data recorded from 5 subdermal electrodes placed in a symmetrical frontal-mastoid montage. A continuous online EEG tracing was obtained with a simultaneous printout of the CSA with SEF in 2 sec epochs. An **ischemic EEG event (IEE)** was defined as: >33% amplitude attenuation of the EEG (compared to both the other hemispheric tracing and earlier recordings) sustained >30 sec (2) and/or; a unilateral decrease in the SEF to <50% of its average value (over the preceding min) sustained >30 sec (1). The **duration of an IEE** was defined as: the time (min $\pm$ 30 sec) from the initial decrease in amplitude/SEF until the onset of amplitude/SEF recovery to baseline. The duration of all IEEs detected were summated for each patient to give the **cumulative ischemic EEG time**.

The decision to place a shunt was based on the above definition of an IEE. Data analysis was performed using Fisher's Exact Test and a $p<0.05$ was considered significant.

Results: In 103 CEAs, 26 IEEs were detected in 20 patients (19.4%). A.) 4 patients had an IEE during hypotensive episodes. All recovered with therapy in <3 min and the patients awoke without new deficits. B.) 14 IEEs occurred **Early**, within 7 min of clamping, and all resolved 1-2 min after shunt placement (13.6%). Average time to shunt placement was 3 min (range 2-7 min). C.) 8 IEEs were detected **Late** during arteriotomy closure, 6 in patients who had received a shunt due to an Early IEE and 2 in nonshunted patients. 7 of these 8 Late IEEs recovered after clamp removal, but 4 of the 7 patients awoke with new deficits which resolved in <12 hrs. The eighth Late IEE did not recover after unclamping. This occurred in a patient who awoke with a new deficit which was permanent.

Overall, 6 new postoperative deficits (5.8%) occurred, 5 in patients whose cumulative ischemic EEG time was $\geq$ 9 min (Table 1). 5 of the 6 new deficits were transient, resolving within 12 hrs. The sixth deficit, which was permanent (%CVA=1%), was found in the patient with the longest cumulative ischemic EEG time (15 min). 1 of the 5 transient deficits occurred in a patient in whom no IEEs were noted. In addition, there was 1 patient who awoke neurologically intact despite a cumulative ischemic EEG time of 9 min. Data analysis demonstrated a highly significant association between cumulative ischemic EEG time and neurological outcome in: 1.) All 103 patients (Table 1) and; 2.) the 35 patients with a prior history of CVA (Table 2).

Discussion: Our results indicate that the 2 channel CEEG can be used during CEA to reliably detect the presence of cerebral ischemia which requires shunt placement during clamping. Furthermore, the cumulative ischemic EEG time appears to correlate with the postoperative neurological outcome in patients both with and without a prior history of CVA. The previous investigators (1) used a univariate descriptor, SEF, alone to define IEEs. When looking for subtle EEG changes univariate descriptors have proven unreliable (3). Our study suggests that detection of intraoperative cerebral ischemia with the 2 channel CEEG is best facilitated by continuous monitoring and familiarity with the raw EEG tracing combined with one or more of the descriptors available to the anesthesiologist.

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TABLE 1: CUMULATIVE ISCHEMIC EEG TIME VS POSTOP NEUROLOGICAL OUTCOME—ALL PATIENTS (N=103)

POSTOP EXAM	CUMULATIVE ISCHEMIC EEG TIME 0 TO <9 MIN	 9 OR > MIN
Intact	96	1
New Deficit	1	5[a]

$p<0.0001$

TABLE 2: CUMULATIVE ISCHEMIC EEG TIME VS POSTOP NEURO OUTCOME—PRIOR CVA PATIENTS (N=35)

POSTOP EXAM	CUMULATIVE ISCHEMIC EEG TIME 0 TO <9 min	 9 OR > MIN
Intact	30	1
New Deficit	1	3[a]

$p<0.003$

[a] Patients with Late IEE during arteriotomy closure

Title: ANALYSIS OF HUMAN EPIDURAL PRESSURES

Authors: PS Thomas, M.D., JI Gerson, M.D. and GA Strong, M.D.

Affiliation: Department of Anesthesiology, State University of New York Health Science Center at Syracuse, Syracuse, New York

Introduction. Although epidural entry pressure has been identified as negative,[1,2] little is known of the change in baseline epidural pressures with demographics, the time course of pressure change with injection (compliance curve), occasional difficulty in obtaining negative entry pressure, or the temporal relation of the epidural pressure wave to arterial and venous pressures. Preliminary findings of an on-going informed consent study approved by the Human Protection Committee in 35 patients undergoing epidural blocks for various pain syndromes are reported.

Methods. Lumbar epidurals with 0.25% bupivicaine and continuous EKG monitoring were performed in the lateral position by the same physician. All resulted in development of sensory and sympathetic, but not motor blockade. The saline-filled recording system consisted of an 18 gauge Tuohy needle connected (from patient to recorder) to a stopcock holding a Macintosh balloon filled with 0.5cc of saline, a second stopcock with two branches to (1) 4 ft. of pressure tubing, 10cc syringe on an automatic injector and (2) 2 ft. of pressure tubing, a stop-cock and a Hewlett-Packard pressure transducer and recorder. This allowed sequential measurements of epidural space pressures after initial Macintosh balloon-guided identification of the space and after injections of a 2cc test and 6cc doses of anesthetic. Zero reference was the level of the spinous processes. Base pressure was defined as the pressure in the space 3 minutes after the identification of the space by balloon collapse. Data were analyzed using ANOV, linear regression and T-test with $P < .05$ considered significant.

Results. The system's damped natural frequency was 14 Hz, with a 0.16 damping coefficient. 34/570 pressure values $>$45mmHg were off-scale and reported as 45mmHg. Base pressure in all patients (except one) was positive (-1 to 16.5 with mean ± SD 7.89 ± 4.1), and increased to 8.2 ± 4.0 at 3 minutes after 2cc injection and to 8.9 ± 4.5 at 3 minutes after 6cc injection ($P < .04$).

DEMOGRAPHIC DATA

Variable	Value	Base Pres. Effect
Weight (lbs)	156 + 30 (s.d.)	None
Height (inch)	65.5 + 5.1 (s.d.)	None
Sex	18M, 17F	None
Past laminectomy	6 +, 29 - (12.8 ± 2.8, 7.0 ± 3.7)	$P < 0.005$

The base pressure in patients age $\geq$ 50 (n=10) was (6.2mmHg) and significantly lower than age $<$ 50 (n=25) 8.5mmHg. For all patients, log transformation of the 2cc and 6cc compliance curves yielded slopes not significantly different: -0.0022 ± 0.0002 log mmHg/sec (combined) (Fig. 1); nor did compliance curve slopes differ between patient age groups. We report intra-arterial, central venous, and epidural pressures in a single patient (Fig. 2).

Discussion. Contrary to Usubiaga, et al,[2] we found generally positive baseline pressures and no change in baseline pressures or compliance curves in patients $>$50 vs. $<$50. We avoided recording "entry" pressures because of operator muscular artifact and noted spurious "negative pressure" if the Tuohy needle was incompletely filled. If underlying equilibrium pressure is sufficiently positive, as in our study population, "tenting the dura" may not produce negative pressure. The peak of a typical epidural tracing occurred at the peak of the arterial trace, not the CVP. This was timed by the EKG in every patient, and the arterial pressure trace in one.

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Fig. 1

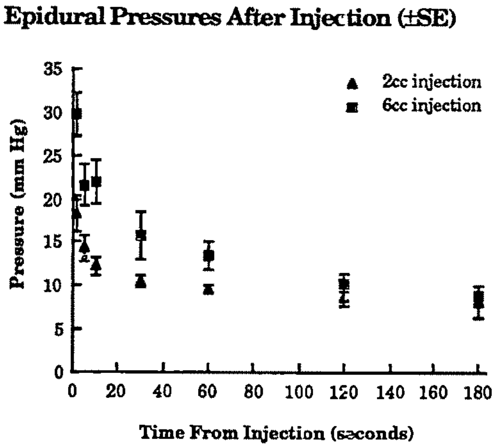
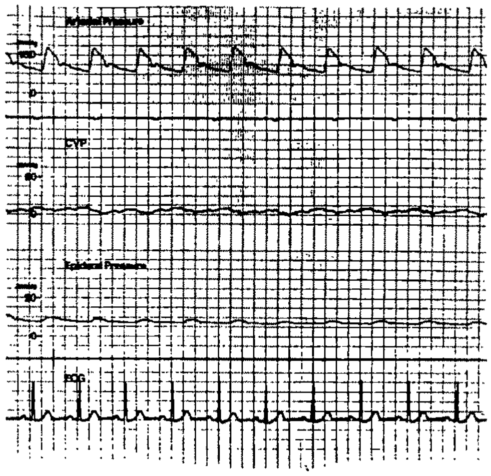


Fig. 2



TITLE: **CENTRAL VEIN LOCALIZATION WITH A TRANSDUCED NEEDLE**

AUTHORS: TC Thomas, M.D., CF Ward, M.D., NA Kennelly, B.S., FR Trousdale, B.S.

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INTRODUCTION: Unintentional arterial puncture is a well-described complication of percutaneous cannulation of the central venous system. In numerous situations, this puncture is difficult to accurately recognize, due either to the use of small bore needles, pre-existing patient cyanosis, or significantly elevated central venous pressure. We propose a method of reliably differentiating between arterial and venous puncture with no additional steps to the procedure.

METHODS: A pediatric I.V. T-piece extension (Abbott Extension Set with "T" No. 4612) was attached to a transducer via a length of high-pressure tubing. The rubber injection port on the female end of the T-piece was removed and a slip-fit syringe was attached, while the finder needle was placed on the male end of the same T-piece. The entire system was then flushed with gas bubble-free heparinized saline. The central vein was identified with the finder needle, which was in turn substituted for an 18 or 20 gauge thinwall needle which accommodated the appropriate sized guide wire. The wire can be passed through the T-piece into the needle if so desired.

RESULTS: Following vessel puncture, the pressure waveform of that vessel appears on the monitor screen, with fidelity somewhat dependent on the bore of the needle in use. Over the range of 25 to 18 gauge, venous puncture has been most obviously identified by the appearance of a low (<20 mm Hg) waveform that varies with cardiac and respiratory cycle (Fig. 1). Larger gauge needles obviously present better waveform detail (fig. 2). Arterial puncture is best identified by the necessity to change measurement scales when the 40 mm Hg pressure scale limit is exceeded by arterial pressure that varies minimally with respiration (Fig. 3--Note 0-200 mm Hg pressure scale).

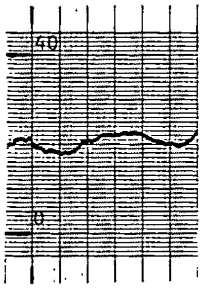

Fig. 1

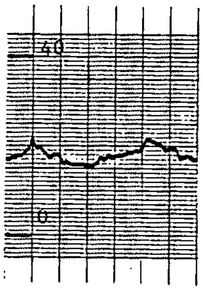

Fig. 2

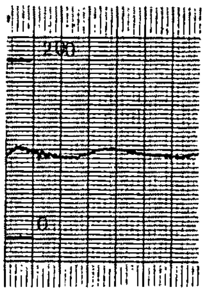

Fig. 3

The technique may fail in several ways: a) arterial puncture seen as venous, b) venous puncture seen as arterial, or c) uncertain localization with useless screen presentation. Over an initial series of 30 patients, no type a or b failures have occurred, while one type c failure has occurred.

DISCUSSION: Numerous methods for identifying unintentional arterial puncture have been described[1,2]. The number attests to the unreliability of any single method, especially if additional procedural steps are undesirable. The method described here has a very high degree of reliability with no additional steps involved, and adds the additional time saving feature of allowing on-demand syringe refill with clear saline whenever the operator so requests. It has been found to be especially useful for clarifying vein puncture with small bore needles in children with central shunts that produce both decreased saturation and elevated central venous pressure.

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Title: AN INITIAL STUDY OF ROPIVACAINE FOR EPIDURAL ANESTHESIA

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Introduction

Ropivacaine, a congener to mepivacaine and bupivacaine, has been widely studied in laboratory animals. We did the first human injection of the drug for regional anesthesia, in this country, on March 25, 1988. This report concerns clinical and pharmacologic data from that landmark patient and others who participated in a study of epidural anesthesia.

Methods

The study was approved by the Institutional Review Board. Fifteen patients gave informed consent for epidural anesthesia with 20 ml of ropivacaine. All patients were between the ages of 18 to 60, ASA Class 1 or 2, and were having orthopedic procedures of the lower extremity. The first five patients received 0.5% ropivacaine, the second five 0.75% ropivacaine, and the third five 1.0% solution. A single injection technique was used after identifying the epidural space at L2-3 or L3-4. An initial test dose of 3 ml of 1.5% lidocaine, with 1:200,000 epinephrine, was given to each patient. After 3-5 minutes, 20 ml ropivacaine dose was given in 5 ml increments over a 2 minute period. Onset of block was checked by pin-prick (sensory) and the Bromage scale (motor) at 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes. Peripheral venous blood samples were drawn at similar times and over the first 12 hours to determine plasma levels of ropivacaine. Cardiovascular changes (heart rate, ECG, and blood pressure) were monitored continuously with automatic recorders. The quality of anesthesia, tourniquet pain, and any other subjective or objective responses of the patient were monitored by the anesthesiologist. The duration of the block was monitored as noted above for onset. A series of basic laboratory tests (hematology, blood chemistry), 12 lead ECG, and neurologic assessment were done preoperatively and again on the first postoperative day.

Results

The drug provided effective analgesia in all patients. The onset time, duration, block height, and degree of motor block are presented in Table 1. Three patients experienced tourniquet pain, but two of these occurred more than 5 hours after administration of the block. The duration of pain relief in each of these patients, having major orthopedic procedures, was consistently prolonged after the complete return of motor function. There were no dysrhythmias and no unexpected changes in heart rate or blood pressure. There was no evidence of persistent neurologic changes induced by the drug. Plasma concentrations of ropivacaine were all under the 2 ug/ml range.

Discussion

Ropivacaine is an effective local anesthetic drug when used for epidural anesthesia in humans. It is distinctly longer acting than bupivacaine. This finding in humans is in contrast to the findings in laboratory animals. Its time of onset is similar to bupivacaine. Blood levels of the drug are well within the safe range and peak levels were less than 2 ug/ml of plasma. Cardiovascular changes were compatible with those associated with the autonomic blockade of epidural anesthesia. There was no evidence of cardiac irritability or myocardial depression. It has good differential with regard to sensory vs. motor block, and therefore appears quite promising in clinical scenarios that demand good analgesia--e.g., obstetrics and pain control.

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TABLE 1

Ropivacaine Concentration	Average Onset Time (mins)	Average Block Height	Degree of Motor Block (ala Bromage)	Time to Regression to T12 (hrs)	Total Duration of Sensory Block (hrs)
0.5%	3.6	T5	1.2	* 4.4 ± 1.7	* 5.75 ± 1.8
0.75%	2.0	T4	2.6	5.8 ± .75	8.1 ± .89
1.0%	3.2	T4	3.0	5.9 ± .80	7.6 ± .96

* Values are mean ± 1 SD

Title: A DOUBLE BLIND COMPARISON OF THE EFFECTS OF LABETALOL AND NITROPRUSSIDE ON SHUNT FRACTION DURING DELIBERATE HYPOTENSION

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Introduction: Sodium nitroprusside(N) is the drug most commonly utilized to produce deliberate hypotension during anesthesia. Its use can be associated with several adverse effects including an increase in pulmonary shunt of 4-5% (1) which is probably related to an inhibition of HPV. Recent studies suggest that labetalol(L), when combined with isoflurane, is useful to induce hypotension (2). The purpose of this study was to compare, in a double blind fashion, the pulmonary effects of N and L when utilized to produce controlled hypotension for major spine surgery.

Methods: 19 ASA Class I-II patients gave their informed consent to participate in this IRB approved protocol. Patients were excluded if they had a history of myocardial infarction within 6 months, congestive heart failure, hypertension, bradycardia < 55 bpm, heart block > 1°, clinically significant hematologic or hepatic disease, Cr > 2.5 mg%, and COPD. Monitors other than those standardly used, consisted of an arterial catheter, pulmonary artery catheter, and electroencephalogram (Lifescan EEG). Anesthetic technique was standardized and consisted of premedication with morphine 0.8 mg/kg and atropine sulphate 0.4 mg IM. Induction was with thiopental 4-6 mg/kg and fentanyl 3-5 μg/kg. Endotracheal intubation was facilitated with succinylcholine 1 mg/kg. Maintenance consisted of N_2O 60-70% in O_2 30-40% and isoflurane at an end tidal concentration of 0.6-0.7%. Muscle relaxation was maintained with vecuronium 0.05 mg/kg. At the surgeons request hypotension was induced with either a N infusion or L bolus. Every patient received an infusion and bolus however only active drug by one route and normal saline via the other. N was prepared as 0.02% solution and infusion initiated at 0.2 μg/kg/min and increased until goal blood pressure was achieved (MAP of 55-60 mmHg). L was administered as 10 mg increments every 10 minutes until goal blood pressure was achieved or a maximum of 300 mg had been given. BP, (systolic, diastolic and mean) HR, pulmonary artery systolic, diastolic and mean pressure, pulmonary artery occlusion pressure, CVP, and CO were measured post induction, pre hypotension, at initial goal hypotension, every 15 minutes thereafter, on request to return to baseline and every 15 minutes until baseline values were achieved. Also obtained at these times were arterial and mixed venous gases to determine right to left shunt fraction and changes in shunt fraction with induction of hypotension. ABG samples were collected and analyzed on a Radiometer ABL 330 analyzer which was calibrated prior to each case. A standard shunt formula was used for calculating the shunt fractions which includes $\dot{V}/\dot{Q}$ contribution as well as true shunt. Temperature corrections were made for PaO_2, $PaCO_2$ and water vapor pressure. Data was analyzed using ANOVA with repeated measures. A $p < 0.05$ was considered significant.

Results: There was no difference in the demographics between the two groups. Shunt measurements were obtained on 15 patients at baseline pre hypotension (i.e. on surgeons request to begin hypotension), at goal (MAP=55-60 mmHg), 30, 60 and 60 minutes after discontinuation of medication. Data analysis revealed significant differences in the N group not present in the L group. With the induction of hypotension there was 111% increase in shunt fraction in the N group as compared to a 5.9% increase in the L group. Subsequently shunt continued to increase and was 151% greater than baseline values at 60 mins(Fig. 1). The L group showed no significant increase in shunt. There was no significant difference in mean pulmonary artery pressure over this time period.

Discussion: The shunt fractions in this study were generally similar to those reported by others in anesthetized individuals (1,3) although lower values were seen in the L group and N baseline. This is most likely attributable to the fact that our values were obtained in the prone position known to result in improved $\dot{V}/\dot{Q}$ matching (4) as opposed to the supine position. Several authors have shown that induced hypotension with N results in an increase in shunt (1,5). Casthely and colleagues reported that this increase in shunt might affect pulmonary gas exchange in patients without lung disease. Similarly we found that N administration significantly increased shunt fraction when utilized to induce hypotension. These changes are not apparent with L administration. The values seen for shunt fraction after administration of N are small and did not result in significant physiologic impairment in these healthy patients in the prone position. In a more compromised patient in the supine position, these changes could be more pronounced and L might be a better choice.

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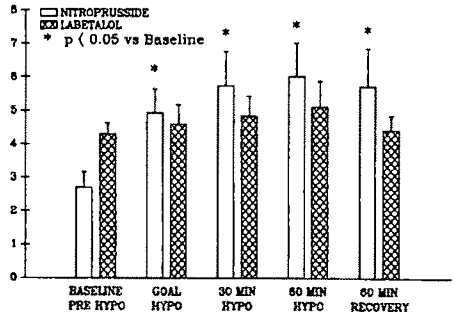
INTRA OPERATIVE RIGHT TO LEFT SHUNTING WITH LABETALOL AND NITROPRUSSIDE



Title: COMPARATIVE EFFECTS OF ESMOLOL AND VERAPAMIL IN A MODEL OF SUPRAVENTRICULAR TACHYDYSRHYTHMIAS

Authors: KJ Tuman, M.D., CA Wong, M.D., RJ McCarthy, Pharm.D., AM LaBarge, B.S., and AD Ivankovich, M.D.

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Introduction. Supraventricular tachydysrhythmias (SVT) are a commonly encountered clinical problem after cardiothoracic surgery. Current drug therapy options for acute management of this problem include intravenous verapamil (V) and esmolol (E). V inhibits slow inward calcium currents and E blocks beta adrenergic receptors, both producing negative dromotropic effects - slowing conduction through and increasing the refractoriness of the atrioventricular node. This study was performed to compare the effects of E and V on systemic hemodynamics, coronary perfusion and myocardial contractility at doses which decreased the ventricular rate in a model of SVT.

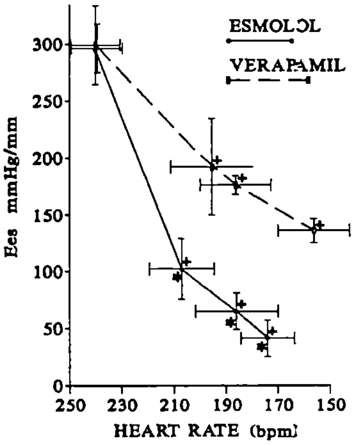
Methods. With approval of the institutional animal care committee, 10 pentobarbital anesthetized dogs were intubated and ventilated to maintain normocarbia ($FIO_2 = 1.0$). After a transverse thoracotomy, noncannulating electromagnetic flow probes were placed around the ascending aorta and proximal LAD coronary artery, and 2 piezo-electric crystals were placed 1 cm apart, in the endocardium, perpendicular to the midpoint of a line drawn from the aortic root to the LV apex. LVEDP was measured directly via the LV apex. Aortic pressure was measured above the aortic valve via the carotid artery. End systolic pressure-end systolic length (ESP-ESL) measurements were recorded and analog signals digitalized at 200 Hz using a microcomputer. The ESP-ESL points lie on a line whose slope (Ees) reflects contractility and is independent of changes in pre- and afterload (1). Ees was calculated by linear regression of ESP-ESL pairs generated during 5-7 sec thoracic aortic and inferior vena caval snare occlusions. Rapid atrial stimulation delivered via pacing wires to the left atrial appendage (800 pulses/min) at 20 mA produced an irregularly irregular rate. 5 dogs received E (0.5 mg/kg followed by 50 mcg/kg/min for 10 min, then another 0.5 mg/kg followed by 100 mcg/kg/min for 10 min, then another 0.5 mg/kg followed by 200 mcg/kg/min for 10 min). 5 dogs received V (60 mcg/kg followed by 1 mcg/kg/min for 10 min, then 60 mcg/kg followed by 2 mcg/kg/min for 10 min, then 60 mcg/kg followed by 4 mcg/kg/min for 10 min). Values for HR, MAP, CO, coronary blood flow, LVEDP, Ees and SVR were determined before drug infusion and then 10 min after each of the 3 levels of drug. The effects of E and V on the former variables were compared with analysis of variance for repeated measures and the null hypochesis rejected if $p < 0.05$.

Results. Hemodynamic variables did not differ between groups before drug administration. Ventricular rate decreased progressively with increased infusions of each drug and there was no difference in HR between corresponding infusion levels of E vs V. Progressively increasing doses of E and V were both associated with significant and progressive decreases in contractility (Ees) compared to baseline. E produced significantly greater decreases in contractility than V at doses which produced similar degrees of atrioventricular conduction blockade (see Figure).

This resulted in decreases in CO and increases in SVR compared to baseline in animals receiving E, while CO and SVR did not change in animals receiving V. These changes in SVR may in part be reflexly related to decreased CO or to increased peripheral arteriole tone seen with beta adrenergic blockade and not seen with calcium entry blockers which tend to dilate vascular smooth muscle. MAP tended to increase from baseline as HR slowed in both groups. Coronary blood flow, coronary perfusion pressure and LVEDP did not change from control values in either group.

DRUG LEVEL		0	1	2	3
HR (bpm)	E	237±12	204±17	183±20	171±14
	V	237±15	198±14	183±18	153±17
CO (l/min)	E	2.74±.41	2.13±.46	1.94±.45	2.35±.41
	V	2.74±.44	2.79±.46	2.67±.50	2.38±.26
MAP (mmHg)	E	79.4±3.4	82.4±4.3	94.6±5.9	96.2±9.3
	V	71.2±5.4	76.2±6.5	77.6±9.6	80.2±6.0
SVR(dyne·cm·sec^{-5})	E	1712±239	2601±770	2658±620	2590±546
	V	1697±513	1639±200	1733±215	1998±247
LVEDP (mmHg)	E	5.4±1.5	7.0±1.7	5.4±1.4	5.1±1.7
	V	4.4±0.8	3.3±1.7	4.3±1.9	2.8±1.1
LAD flow (ml/min)	E	24.4±8.1	21.2±5.5	26.2±5.0	27.6±7.2
	V	22.4±5.5	22.2±4.5	22.4±4.1	24.4±5.4

values are means ± SEM



* — p<0.05 COMPARED TO VERAPAMIL AT THESE TIMES
+ — p<0.05 COMPARED TO BASELINE WITHIN GROUP
VALUES ARE MEAN ± SEM

Discussion. E and V were both effective in decreasing ventricular rate in this model of rapid SVT. Neither drug produced significant effects on coronary blood flow or perfusion pressure when used for control of ventricular rate during SVT. Based on the load insensitive measure of contractility, Ees, for a given degree of negative A-V nodal dromotropic effect, V appears to have less negative inotropic effect than E. Conversely, for the same degree of myocardial depression, V was more efficacious than E in blocking A-V nodal conduction of rapid supraventricular stimuli. This may have important clinical implications in the management of patients with impaired ventricular function who develop SVT after cardiothoracic surgery.

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Title: CONTINUOUS INFUSION OF SUFENTANIL AND MIDAZOLAM FOR CORONARY ARTERY SURGERY

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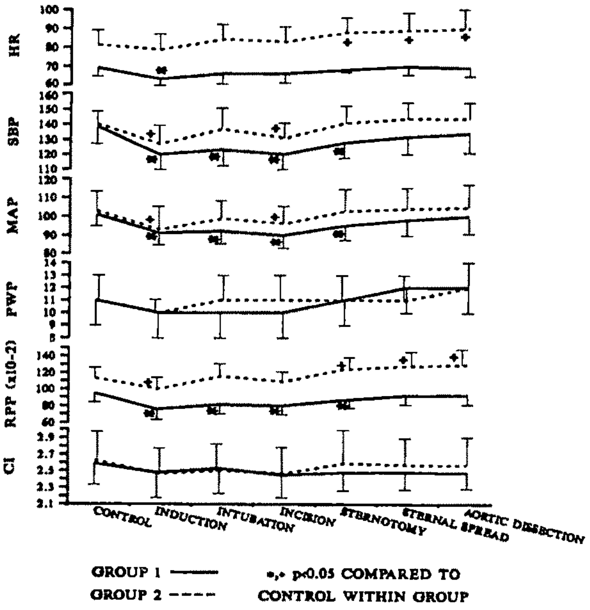
Introduction. Preservation of hemodynamic stability and myocardial oxygenation during anesthetic induction and the period before cardiopulmonary bypass (CPB) are required for patients undergoing coronary revascularization (CABG). However, patients with good left ventricular function are at risk for hyperdynamic responses with high-dose narcotic anesthesia. Sufentanil blunts preCPB hyperdynamic responses better than fentanyl (1), but large doses of sufentanil for induction of anesthesia may be accompanied by hypotension (2). Addition of volatile or intravenous anesthetics to moderate doses of narcotics may attenuate hyperdynamic responses in the preCPB period. We hypothesized that the combination of midazolam (M) with sufentanil (S) infused at moderate doses would provide stable hemodynamics and minimize stress responses in patients with good LV function undergoing CABG.

Methods. After Institutional Human Investigation Committee approval and informed consent, 30 ASA III or IV patients undergoing CABG participated in this study. Excluded were emergent procedures, severe ventricular impairment, accompanying valve disease or LV aneurysm. Preoperative beta blockers (BB) and calcium channel blockers (CCB) were continued until surgery. 15 patients (Group 1) were receiving BB, CCB and nitrates, while 15 patients (Group 2) received only CCB and nitrates preoperatively. Morphine 0.15 mg/kg with scopolamine 0.4 mg IM were administered 1 hr prior to insertion of femoral arterial and pulmonary artery catheters. Standard limb and V5 ECG leads were monitored for ST segment changes during the study period. Anesthesia was induced with pancuronium (P) 0.02 mg/kg followed 2 minutes later by infusion S 2 mcg/kg and M 0.1 mg/kg over 5 minutes with 0.15 mg/kg of P. After intubation and controlled ventilation (100% O_2), anesthesia was maintained using a continuous infusion of 0.7-1.5 mcg/kg/hr of S and .07-.15 mg/kg/hr of M (100:1 mixture of M:S). The rate of infusion was titrated to maintain MAP within 20% of baseline. If MAP exceeded baseline values by > 20% for >5 min despite changes in infusion rate, nitroglycerin was administered. Hemodynamic parameters were recorded or calculated at the following intervals: before and after induction, after intubation, incision, sternotomy, sternal spread and during aortic dissection. Hemodynamic data were compared using ANOVA with repeated measures in one variable. Post-hoc tests were done using the Tukey-a method. Demographic data, incidence of ischemia and need for vasodilator were compared with t-tests and χ^2 analysis where appropriate. $P < 0.05$ was considered significant.

Results. There were no significant differences between group means for age, ejection fraction, # of grafted vessels, body surface area or cardiac medications except for BB. None of the patients had renal, hepatic or pulmonary disease. Beta blocked patients had significantly lower baseline HR and RPP than non beta blocked patients. Baseline values of MAP, PWP and CI did not differ between groups. Compared to baseline, HR was decreased after induction in Group 1, while it increased after sternotomy, sternal spread and Ao dissection in Group 2. SBP and MAP were less than control levels after induction, intubation, incision and sternotomy in Group 1, and less than control levels after induction and incision in Group 2. This resulted in a RPP less than control after induction, intubation, incision and sternotomy in Group 1 and after induction in Group 2, however RPP exceeded control values after sternotomy, sternal spread and Ao dissection in Group 2. There were no significant changes in RAP, PWP, mean PA, CI, SI, SVR, PVR, LVSWI, RVSWI from baseline in either group. 4 of 15 patients in Group 2 required vasodilators for BP control, compared to 0 of 15 in Group 1 (NS). 2 of 15 patients in Group 1 versus 3 of 15 in Group 2 developed ischemic ECG changes before CPB (NS); one of these Group 2 patients had a postop MI.



Discussion. This study demonstrates that the combination of sufentanil with midazolam infused at moderate doses provides a consistent depth of anesthesia with stable hemodynamics for patients with good ventricular function undergoing coronary revascularization, by avoiding the hypotension associated with high dose of S (2) and decreasing the hyperdynamic responses seen when narcotics are used alone. The incidence of hypertension after sternotomy and sternal spread are less with this technique than when sufentanil is used alone (1,3). The study also emphasizes the advantages of preoperative beta adrenergic blockade. Hypertension requiring vasodilator supplementation never occurred in beta blocked patients, and beta blockers attenuated the small rises in HR and RPP seen after sternotomy, sternal spread and aortic dissection in non-beta blocked patients.

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Title: POSTOPERATIVE MYOCARDIAL INFARCTION: IMPORTANCE OF CALCIUM ENTRY AND BETA ADRENERGIC BLOCKING DRUGS

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Introduction. Chronic preoperative treatment with calcium entry blockers alone or in combination with beta adrenergic blockers may not have a beneficial effect on the occurrence of intraoperative myocardial ischemia (1). Although there is a strong association between intraoperative ischemia and postoperative myocardial infarction, only the minority of episodes of intraoperative ischemia result in postoperative myocardial infarction (2,3) and not all cases of postoperative myocardial infarction have documented intraoperative electrocardiographic evidence of ischemia. Therefore, we postulated that calcium entry blockers might have a beneficial effect on the occurrence of postoperative myocardial infarction after coronary revascularization even though other studies have reported that calcium entry blockers may not effect the overall incidence of intraoperative ischemia.

Methods. After approval of the institutional Human Investigation Committee, 803 consecutive patients free of signs of congestive heart failure, undergoing coronary revascularization were prospectively studied. Anesthesia consisted of narcotic based techniques supplemented with volatile agents as required. All preoperative antianginal therapy was continued up to the morning of surgery. Intraoperative hemodynamic aberrations exceeding 20% of baseline values, dysrhythmias and ischemia were controlled by pharmacologic means. Ischemia after cardiopulmonary bypass and throughout the ICU stay was diagnosed on calibrated paper recordings as horizontal or downsloping ST segment depression of at least 0.1 mV extending at least 80 msec beyond the J point of the QRS complex, postoperative myocardial infarction as new significant Q waves in the postoperative ECG and CKMB > 80 IU/l; mortality was defined as in-hospital death. For data analysis, patients were divided into 3 groups based on their chronic preoperative antianginal therapy. Group I: patients not receiving calcium entry blockers, Group II: patients chronically receiving calcium entry blockers, Group III: patients chronically receiving both calcium entry blockers and beta adrenergic blockers. Chi-square tests and one way ANOVA were used where appropriate to compare the following characteristics between groups: age, presence of unstable angina, significant left main coronary artery stenosis, poor LV function (ejection fraction < 0.45 or LVEDP > 18 torr), diabetes, reoperation, recent preoperative myocardial infarction (< 3 months), use of nitrates, ischemic clamp time, # of vessels revascularized, HR > 110 bpm, hypertension or hypotension exceeding 20% of baseline and requiring vasoactive infusions, and need for intraortic balloon counterpulsation after cardiopulmonary bypass. The relative influence of these variables plus the use of calcium entry blockers and beta adrenergic blockers on the outcome variable of postoperative myocardial infarction was tested by multivariate discriminant analysis using the Wilkes-Lambda method. Chi square tests were used to compare the incidence of postoperative electrocardiographic signs of ischemia, myocardial infarction and death between groups. The null hypothesis was accepted when p exceeded 0.05.

Results. There were no significant differences in the 14 patient variables listed above between groups except for left ventricular dysfunction (Group I: 56.3%, II: 61.9%, III 46.6%). There was a significant difference in the incidence of postoperative ischemia and postoperative myocardial infarction between the 3 groups. Patients receiving calcium entry blockers had significantly less postoperative myocardial infarction than those not receiving calcium entry blockers; those receiving both calcium entry blockers and beta adrenergic blockers had the lowest incidence of postoperative myocardial infarction.

	Group I n=141	II n=430	III n=232	Overall n=803
% postop ischemia*	33.3	25.8	17.2	24.7
% postop MI*	9.2	4.7	2.6	4.9
% death	0.7	1.9	1.7	1.6

* $p < 0.05$ between groups

When controlling for ventricular dysfunction, use of calcium entry blockers was still associated with less postoperative myocardial infarction, especially when combined with beta adrenergic blockers.

	Group I	II	III
LV dysfunction			
absent - % PMI	7.9 (63)	5.5 (165)	2.4 (124)
present - % PMI *	10.3 (78)	4.2 (265)	2.8 (108)

*$p < 0.05$ between groups
value in ( ) is n for group.

Multivariate discriminant analysis revealed that hypotension requiring vasopressors, recent preoperative myocardial infarction, prolonged cross clamp time, non-use of calcium entry blockers, advanced age, reoperation, significant left main stenosis and non-use of beta adrenergic blockers were significantly related to the occurrence of postoperative myocardial infarction; the remainder of the variables were nonsignificantly related.

Discussion. This study demonstrates the beneficial effect of calcium entry blockers on the occurrence of postoperative myocardial infarction after coronary surgery, especially when combined with beta adrenergic blockers. This effect may be related to improved coronary flow after revascularization because of calcium entry blocker mediated reduction of coronary (and graft) spasm or to other mechanisms unrelated to coronary dilation. The lack of effect on intermediary (process) variables such as intraoperative electrocardiographic ischemia in other studies (1) does not necessarily translate to outcome variables such as postoperative myocardial infarction. Maintenance of preoperative antianginal therapy with calcium entry blockers and beta adrenergic blockers appears to have a significant impact on outcome after coronary artery surgery.

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Title: NONINVASIVE MONITORING OF CARBON DIOXIDE IN NON-INTUBATED POSTOPERATIVE PATIENTS: COMPARISON OF PaCO$_2$ VERSUS EtCO$_2$ AND PaCO$_2$ VERSUS TcCO$_2$

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Introduction: The traditional monitoring of respiratory function in non-intubated patients relies on clinical observation, intermittent arterial blood gas sampling and pulse oximetry all of which have major limitations. Clinical signs and symptoms of depressed ventilatory function may not be evident until severe hypoxia and/or hypercarbia occur. Arterial blood gas sampling is invasive; not without complication; intermittent in nature and often associated with delay in reporting. Patients receiving increased FIO$_2$ may not desaturate despite the presence of alveolar hypoventilation and an increased PaCO$_2$. EtCO$_2$ measurement is extensively used in intubated patients as a continuous noninvasive approximation of PaCO$_2$ but its use in non-intubated patients has been associated with technical difficulties. Transcutaneous carbon dioxide (TcCO$_2$) measurement has been used in neonates but infrequently in adults. The purpose of this study was to examine the relationship of PaCO$_2$ to EtCO$_2$ and TcCO$_2$ in postoperative non-intubated adults.

Materials and Methods: The study was approved by the Human Experimentation Committee of the Toronto General Hospital. Twenty-three patients having given informed consent and requiring arterial line monitoring were studied in the recovery room after extubation. Each patient received supplemental oxygen by face mask. EtCO$_2$ was measured continuously through a 2 in. #16 guage IV cannula inserted into modified Intertech^R nasal prongs such that the cannula tip was positioned between the two prongs. The oxygen delivery tube of the nasal prongs was occluded to prevent aspiration of room air. The gases were analyzed by a calibrated Puritan Bennett^R 254 Airway Gas Analyzer having both a digital and wave form display of EtCO$_2$. EtCO$_2$ values were the average of five consecutive breaths where the wave form had a flat plateau (indicative of expired alveolar gas). TcCO$_2$ values were obtained using a calibrated Kontron 634 Cutaneous PCO$_2$ monitor with a sensor temperature of 44°C. The sensor membrane was charged weekly or earlier if damaged. A 15 minute equilibration time was allowed after sensor placement on cleansed skin below the clavicle. Arterial blood gases were not corrected for patient temperature. PaCO$_2$, EtCO$_2$ and TcCO$_2$ were collected every 30 minutes for the first 3 hours of recovery room stay. Values are reported as means ± SD. Analysis was by linear regression and paired Student's t test.

Results: 143 data sets were obtained for 22 patients: 7 females, 15 males; age 47 ± 21 yr. (range 16-80); weight 73 ± 15 kg: height 168 ± 2.8 cm: length of surgery 4.5 ± 2.8 hr. (range 1.5-13). One male patient was excluded on admission to the recovery room because of almost complete nasal obstruction. There was no significant difference between PaCO$_2$ and EtCO$_2$ (44 ± 5 and 43 ± 6 mmHg respectively, ranges 33 - 57 and 33 - 59). The TcCO$_2$ of 65 ± 9 mmHg (42 - 102) was significantly higher than both the PaCO$_2$ and EtCO$_2$ ($p<0.0001$ for both). There was a good correlation between PaCO$_2$ and EtCO$_2$: PaCO$_2$ = 0.67 EtCO$_2$ + 13.6, r=0.62 ($p<0.001$) SEE=3.16 and PaCO$_2$ and TcCO$_2$: PaCO$_2$ = 1.21 TcCO$_2$ + 11.91, r= 0.69 ($p<0.001$) SEE=4.70. EtCO$_2$ = PaCO$_2$ ± 4 mmHg in 97/143 samples (68%) and ± 8 mmHg in 134 samples (94%). In 3 patients there was an acute fall of greater than 10 mmHg in TcCO$_2$ associated with cessation of shivering during the first 30 minutes in recovery room. In 5 patients there was an acute decrease in EtCO$_2$ of greater than 10 mmHg lasting more than 30 sec. These changes were all associated with a change in capnograph tracing (peaked waveform) and EtCO$_2$ at these times was widely divergent from PaCO$_2$.

Discussion: TcCO$_2$ provided good correlation with PaCO$_2$ but did not offer the advantage of breath to breath analysis. In addition it required a warm-up period, great care in preparing and maintaining the sensor membrane and was subject to fluctuation when shivering was present. This method of measuring EtCO$_2$ utilizing modified nasal prongs is inexpensive, well tolerated by patients, does not interfere with administration of supplemental oxygen by face mask and gives a good approximation of PaCO$_2$ within the range studied provided a plateau is present on the capnograph tracing. The tracing also provides a continuous monitor of respiratory frequency and pattern complimenting the existing use of clinical observation and pulse oximetry in monitoring of non-intubated patients. In addition, it may allow a decrease in the requirement for arterial blood gas sampling.

Title: RESPIRATORY PATTERN IN POST-CAESAREAN SECTION PATIENTS AFTER EPIDURAL OR INTRAMUSCULAR MORPHINE

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Introduction: Epidural morphine for post-caesarean section pain is effective and long lasting. Rare but life threatening respiratory depression after epidural morphine has been reported to occur[1]. More subtle respiratory derangements may also occur and may be related to these episodes of severe respiratory depression. This study was performed to compare the effects of epidural morphine and intra-muscular morphine on post caesarean section respiratory pattern using the respiratory inductance plethysmograph to continuously monitor patients noninvasively for 24 hr. after caesarean section.

Methods: The study was approved by the Institutional Review Board and written informed consent was obtained from all patients. The study was randomized and double blinded. The study population consisted of 23 healthy, term parturients undergoing elective caesarean section with lidocaine epidural anaesthesia. For post-caesarean section pain relief Group 1 received epidural (EP) morphine 5 mg in 10 ml N saline plus 2 ml N saline by intramuscular injection (n=11) and Group 11 received 10 ml N saline epidurally plus 5 mg intramuscular (IM) morphine in 2 ml N saline (n=12). Both the EP and IM doses were given on demand for pain relief with a minimum interval of 30 min between doses. Visual analogue pain scores (VAS) blood pressure and heart rate were measured pre-dose and every 30 minutes for the first hour after each dose and then hourly for the remaining 24 hours. Respiratory pattern and oxygen saturation were monitored continuously for the 24 hr. post-caesarean section period using a respiratory inductance plethysmograph (Respitrace^{R}) and pulse oximeter (Nellcor^{R}). Twenty patients (EP=9/11, IM 11/12) underwent further monitoring while asleep using the Respitrace and pulse oximeter 3-5 days post-operatively when narcotic analgesics were no longer being administered. Apnea (AP) was defined as tidal volume less than 100 ml for greater than 15 sec and slow respiratory rate (SRR) as less than 10 breaths per min for a minimum of 5 min. Data are expressed as mean±SD and were analysed using Analysis of Variance, Student's t, Tukey's and Chi-Square tests as appropriate. $P<0.05$ was regarded as statistically significant.

Results: The groups were similar with respect to age (EP 31±5, IM 33±5 yr), weight (EP 77.6±9.7, IM 74.8±10.6 kg) and height (EP 150±12, IM 163±1.9 cm). VAS was significantly lower (less pain) in the EP group until the fourth dose in the IM group after which pain relief was equivalent in both groups and < 30% of maximum VAS. The IM group received 9.6±2.4 doses (48±12 mg) while the EP group required 1.6±0.7 doses (8±3 mg) ($p < 0.05$). There was no significant difference between groups with respect to incidence of AP or SRR, AP/hr or AP duration (Table 1). Nine of 11 patients in the EP group and 11 of 12 patients in the IM group were monitored during the unmedicated sleep period (control period) (Table 2). Three of 3 patients in the EP group and 3 of 7 patients in the IM group had apneic episodes during both the post-caesarean section and control monitoring sessions (not significant). The lowest oxygen saturation during an apneic period was 94%. Saturation did not fall below 85% for any monitoring period. There was no significant difference in the incidence of nausea (EP 45%, IM 25%) and vomiting (EP 45%, IM 8%) between the groups. There was a greater incidence of pruritis (EP 91%, IM 42%) (p 0.05) in the EP group.

Discussion: Using the inductance plethysmograph and pulse oximeter as non-invasive monitors of respiratory function we were unable to demonstrate any significant difference in incidence of AP or SRR between the two groups. No life threatening alterations of respiratory pattern or desaturation occurred. However due to the occasional and unpredictable occurrence of severe respiratory depression[1] all post-caesarean section patients should be carefully monitored for the first 24 hr.

Table 1: Respiratory Pattern Post-Caesarean Section

	Apnea (n)	Apnea (hr-1)	Apnea (sec)	SRR (n)	SRR (epi)
EP (N=11)	4	0.11±0.08	17.2±1.3	1	3
IM (N=12)	7	0.91±1.83	17.5±1.2	3	32

Table 11: Respiratory Pattern During Control Period

	Apnea (n)	Apnea (hr-1)	Apnea (sec)	SRR (n)	SRR (epi)
EP (N=9)	6	0.29±0.16	18.5±2.4	0	0
IM (N=11)	3	0.56±0.28	17.4±1.0	0	0

N = total patients studied
n = number of patients with AP or SRR
Apnea (hr-1) = Number of apneic episodes/ length of monitoring period
Apnea (sec) = mean duration of apneic episodes
(epi) = episodes

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Title: **MIDAZOLAM-MORPHINE SEDATIVE INTERACTION IN PATIENTS**

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Introduction. A combination of benzodiazepines and opioid drugs are used commonly for intravenous sedation. Life-threatening complications during midazolam-induced conscious sedation in patients receiving opioid drugs have been reported (1) indicating the importance of the problem of midazolam-opioid sedative interaction. Opioid drugs have been shown to strengthen the hypnotic effect of benzodiazepines (2). However, it was not indicated whether the observed results reflected synergism or simple summation of the effects. The aim of the present study was to define the type of midazolam-morphine sedative interaction.

Methods. Ninety unpremedicated ASA physical status I or II adult female patients scheduled for diagnostic curettage or other minor surgeries participated in the study, which was approved by the Institutional Human Investigation Committee. The sedative effect was determined with the use of visual analog self-rating method. The visual analog scale consisted of a 100-mm line without gradation with the word "alert" at the left end and at the right, the word "sleepy." The patients were told to indicate how they felt at the moment by placing a mark perpendicular to the line. Patients were randomly assigned to one of three groups: midazolam, morphine, or midazolam-morphine. Each group consisted of 30 patients divided into six subgroups of five patients each with predetermined doses of drugs in every subgroup. Each patient received two intravenous injections with a 10-minute interval between them. The midazolam group received normal saline and midazolam; the morphine group received morphine and saline; and the midazolam-morphine group received morphine and midazolam. Prior to the first injection and 5 minutes after the second, each patient was asked to mark the visual analog line. Times between injections of drugs and determination of the sedative effect were based on the times to peak effect for these agents (15 minutes for morphine and 5 minutes for midazolam). With combined drug administration, both drugs were injected so that synchronization of the peak effects would occur. These time intervals were selected on the basis of a preliminary study. The self-rated sedation was checked by an investigator who was unaware of what drug(s) or dose(s) was used (double-blind method). The following predetermined doses of drugs each in a subgroup of five patients were administered: in the midazolam group (mg·kg^{-1}) - 0.01, 0.02, 0.03, 0.04, 0.05, 0.07; in the morphine group (mg·kg^{-1}) - 0.03, 0.04, 0.06, 0.08, 0.10, 0.12. In the midazolam-morphine group, doses of both agents were changed from one subgroup to another with the fixed dose ratio of 1:2 (2 mg of morphine per 1 mg of midazolam). This ratio was determined on the basis of the preliminary study and reflects relative sedative potencies of these agents. As a result, the following doses of agents were administered in the midazolam-morphine group (mg·kg^{-1}) - 0.003 and 0.006; 0.005 and 0.010; 0.008 and 0.016; 0.012 and 0.024; 0.02 and 0.04; 0.03 and 0.06. As an endpoint for determining the dose-response curves, a sedation score of 50 mm or more was used, allowing us to obtain a quantal curve of a graded type of response to an agent. As a result, the construction of the dose-response curves and determination of the ED_{50} values were based on probit procedure (3). To define the type of interaction between midazolam and morphine, algebraic fractional analysis (4) was used.

Results. The study groups were comparable with respect to demographic characteristics of the patients. The ED_{50} for midazolam was 0.025 (0.014-0.033) mg kg^{-1} for midazolam and 0.089 (0.072-0.105) mg kg^{-1} for morphine. Comparison of the combined and single-drug ED_{50} doses is presented in the table. In combination, the sum of the fractional doses was not different from a single-drug fractional dose.

Discussion. The midazolam-morphine sedative interaction resulted in a summation. This means that the requirement for one agent to produce a certain degree of sedation is decreased by another agent, but only to a degree equivalent to the sedative dose of the latter. Respiratory and cardiac arrests described in patients who received midazolam in combination with opioids for conscious sedation (1) might be due to the excessive CNS depression caused by a synergistic midazolam-opioid interaction. The results of the present study indicate that the sedative interaction between midazolam and morphine does not go beyond simple summation of the effects. However, this does not exclude the possibility that the interaction between midazolam and morphine in relation to respiratory depression or other adverse effects results in a profound synergism.

Table. Midazolam-Morphine Sedative Interaction

Groups	Fractional Equi-Effective Doses (ED_{50})		
	Midazolam Component	Morphine Component	Sum of Fractions
MDZ	1.00 (0.025)^a	0.00	1.00
MDZ + MPH	0.68 (0.017)^a	0.39 (0.035)^a	1.07 NS
MPH	0.00	1.00 (0.089)^a	1.00

MDZ-midazolam, MPH-morphine. a-in mg•kg^{-1}, NS-deviation from additivity was statistically insignificant.

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TITLE: CLONIDINE POTENTIATES LIDOCAINE-INDUCED EPIDURAL ANESTHESIA

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INTRODUCTION. Clonidine, an alpha$_2$-adrenoceptor agonist has been reported to potentiate spinal morphine analgesia when the two drugs are given intrathecally (1) or epidurally (2). The present study was undertaken to evaluate the effect of clonidine on the quality of anesthesia induced by lidocaine when both drugs were administered epidurally.

METHOD. The study was conducted after institutional approval and informed consents were obtained from all the patients prior to their entry into the study. Forty adult patients scheduled for elective lower abdominal surgeries were enrolled in this study. On the day of surgery all patients were unpremedicated and had indwelling epidural catheters inserted through L_{2-3} lumbar interspace by lumbar puncture with the loss of resistance technique. After the epidural catheter was securely taped in place, the patient was turned to the supine position and 500 ml normal saline was given by rapid intravenous infusion. The patients were then divided into 2 equal groups of 20 patients each in a randomized, double-blind fashion with group 1 receiving epidural administration of 2% lidocaine 20 ml and group 2 receiving epidural administration of 2% lidocaine 20 ml with clonidine Hcl 150 mcg added. After the drug administration, level of sensory loss was tested with pin prick and the time to achieve sensory block at L_1 and T_{10} dermatomes were recorded respectively. The motor block of lower extremities were assessed and recorded using the score system described by Bromage (3). After completion of surgery the time for regression of sensory block to T_{10} and L_1 dermatomes were recorded. Vital signs (blood pressure, heart rate and respiratory rate) were recorded prior to and at every minute after the drug administration up to 15 minutes, then at every 5 minutes for 3 hours. Any untoward effect was also recorded through the 3 hour observation period.

RESULT. The demographic data were similar for both groups (Table 1). As show in Table 2, the onset of sensory block at both L_1 and T_{10} dermatomes were much faster in group 2 than group 1 ($p < 0.001$). Moreover, the duration of anesthesia as measured by the time for sensory block regression to L_1 is significantly longer in group 2 than group 1 ($p < 0.001$). Motor block was more profound in group 2 than group 1 with complete motor block of the lower extremities being observed in 25% of the patients in group 2 versus 5% in group 1. Vital signs remained stable for both groups except for a 10-15% decrease in heart rate in patients in group 2 at 60 to 100 minutes post drug. No significant hypotension or respiratory depression was observed in any of the patients. Side effects were minimal and similar in both groups with more patients experiencing sedation in group 2 than group 1. All patients recovered from the epidural anesthesia without sequela.

DISCUSSION. Clonidine has been shown to produce effective analgesia when administered intrathecally (1) or epidurally (4). It probably exerts its analgesic effect through the activation of the adrenergic receptors in the spinal cord. Our study demonstrated that epidural clonidine when administered concomitantly with lidocaine produced effective anesthesia with a more rapid onset, longer duration of action and a more profound motor block. There was no significant cardiovascular depression or increased side effects associated with such a combination. Recently, much interest has been generated in providing epidural anesthesia with fast onset and more profound block by adding lipid soluble opioids into the local anesthetic solution (5). The combined use of clonidine with local anesthetic appears to be a useful alternative to this aim.

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TABLE 1 DEMOGRAPHICS

	SEX	AGE	HEIGHT	WEIGHT
Group 1	14M 6F	$\bar{x}$ 22.6 yr	$\bar{x}$ 169 cm	$\bar{x}$ 61.9 kg
Group 2	12M 8F	$\bar{x}$ 28.9 yr	$\bar{x}$ 162 cm	$\bar{x}$ 56.9 kg

TABLE 2 SENSORY BLOCK

	ONSET OF SENSORY BLOCK		REGRESSION OF SENSORY BLOCK	
DERMATOMES	L_1	T_{10}	T_{10}	L_1
GROUP 1	11.4±3.5 min	15.5±4.1 min	80±13.1 min	96.5±15.8 min
GROUP 2	6.9±1.8 min	9.9±3.8 min	82.9±23.9 min	125.8±24.4 min

TABLE 3 SIDE EFFECTS

	Nausea	Vomiting	Sedation	Shivering	Urinary Retention
GROUP 1	1	1	0	3	1
GROUP 2	2	2	5	2	2

Title: COMPLICATIONS DURING PRONE POSTERIOR FOSSA CRANIOTOMY IN CHILDREN

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Introduction. There has been much debate over the use of the sitting versus the prone position for posterior fossa procedures. Regardless of position, surgery in this area can cause intraoperative ventilatory difficulty. We have almost exclusively used the prone position for several years. The last reported series of complications in children undergoing prone posterior fossa craniotomy was by Meridy et al in 1974 (1). Anesthetic and surgical techniques have improved since that time. We therefore undertook a retrospective study to examine complications during prone posterior fossa procedures.

Methods. The hospital records of 84 patients who underwent 101 prone posterior fossa craniotomies between January 1983 and June 1988 were reviewed. All procedures were performed 0-15° head up. 10 patients operated on for recurrences had ventriculo-peritoneal shunts in place. 12 other patients had extraventricular drains placed an average of 6.6 days prior to craniotomy.

An inhalational induction was performed in 22 patients, 17 with N_2O/halothane and 5 with N_2O/isoflurane. 6 patients in the halothane group and 1 in the isoflurane group had shunts or drains in place at the time of induction. 73 patients received thiopental, 2 via the rectal route. 6 patients were brought to the operating room intubated and unresponsive. Lidocaine and/or fentanyl supplementation was used in 43 patients. Pancuronium was administered and all patients nasally intubated. Ventilation was controlled to achieve an arterial $PaCO_2$ of 25-32 mm Hg. N_2O was used in 99% of cases with isoflurane in 91% and halothane in 9% of patients. Fentanyl or alfentanil was administered in 53 patients. Central venous pressure and pre-cordial doppler monitoring were not routinely applied.

Results. Intraoperative blood pressure changes were the most common complication. 13 patients had acute hypertension with little or no change in heart rate (HR) in 7 patients, tachycardia in 5 patients, and bradycardia in 1 patient. 3 patients had acute hypotension, 2 patients exhibiting no change in HR and 1 patient with bradycardia. A fourth patient had hypotension secondary to acute blood loss. No ventricular arrhythmias were noted in any patient. The most frequent rhythm disturbance was acute bradycardia seen in 7 patients. Accompanying blood pressure changes were inconsistent with 5 patients showing no change, and hypotension and hypertension each noted in 1 patient. One patient had a run of supraventricular tachycardia requiring treatment with IV propranolol. There were 4 intraoperative cardiac arrests including 2 deaths. 2 patients, a 4 1/2 year old child with a medulloblastoma and a 6 month old infant with a recurrent medulloblastoma, were successfully resuscitated. The 2 deaths both occurred in newborn infants with a congenital teratoma. 4 patients required postoperative intubation and ventilation. 2 of these patients were subsequently found to have bilateral vocal cord paralysis requiring a tracheostomy. The true incidence of venous air embolus (VAE) could not be determined. Only 20 patients had precordial doppler monitoring and of these 2 patients had VAE.

Discussion. Posterior fossa craniotomy is commonly performed in children. In comparing Meridy et al (1) to our series there are striking differences. Ventricular arrhythmias were their most common complication. The absence of ectopy in our series agrees with 2 other studies (2,3) and can probably be attributed to changes in anesthetic techniques since 1974. Acute intraoperative hypertension was our most common problem and it can occur from stimulation of several areas (4). There was no significant difference in morbidity in patients with hypertensive episodes. The only deaths in Meridy et al were non-neurologic in etiology. The 2 deaths in our series occurred in newborn infants. Newborns requiring craniotomy may constitute a high-risk group. In summary, although intraoperative complications are common, few are life-threatening. Prone posterior fossa craniotomy should be considered safe in children with infratentorial tumors.

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Title: THE EFFECT OF CALCIUM CHLORIDE ON PULMONARY VASCULAR RESISTANCE AND RIGHT VENTRICULAR FUNCTION

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Introduction. Right ventricular (RV) function has important implications in overall cardiac performance. In contrast to the left ventricle (LV) which maintains a relatively constant output over a wide range of afterload, the RV is extremely sensitive to increases in afterload. Marked increases in pulmonary vascular resistance (PVR) may be clinically manifested as progressive decreases in RV ejection.(1) This may further deteriorate with RV infarction and RV ischemia, leading ultimately to LV dysfunction due to ventricular interdependence.

Calcium chloride is often administered to patients immediately after separating from cardiopulmonary bypass (CPB) to increase the ionotropic state of the myocardium. Animal studies have shown, however, that even small doses of calcium chloride may result in sustained increases in PVR, precipitating RV failure.(2)

This study was designed to determine the: 1) level of ionized calcium before and after CPB and 2) the effect of the administration of calcium chloride on RV function in patients with normal and elevated PVR.

Methods. Following approval by the Human Investigation Committee, 44 adults (26 men, 18 women, age 64.9 ± 10.3, weight 74.5 kg ± 12.6) scheduled for elective cardiac surgery (37 for coronary artery revascularization, 6 for aortic valve replacement, 5 for mitral valve replacement) were studied. Patients were premedicated with morphine sulfate 0.1 mg/kg and scopolamine 0.005 mg/kg one hour prior to arrival in the operating room. Prior to induction of anesthesia an arterial catheter and pulmonary artery catheter, modified for measurement of right ventricular ejection fraction (RVEF) were inserted. All patients were then anesthetized with fentanyl 40-60 mcg/kg, paralyzed with pancuronium 0.1 mg/kg and intubated. Nitroglycerin at 1 mcg/kg/min was infused throughout the entire operative period. CPB was conducted using a membrane oxygenator, average time 106 ± 35 min. Following separation from CPB patients were kept as controls or received calcium chloride at 5, 10, 15, or 20 mg/kg.

Heart rate, blood pressure, right atrial (RA), right ventricular (RVP), pulmonary artery pressures (PAP), cardiac output (CO), and RVEF were recorded at the following intervals: baseline, 5 min post induction, post-sternotomy, immediately following CPB, 5 minutes following administration of calcium chloride and following chest closure.

Blood samples for the determination of ionized calcium levels were obtained at baseline, immediately prior to separation from CPB, and within 5 minutes of the administration of calcium chloride. All samples were placed in a cold (4°C) tube (without anticoagulant) and measured by a calcium specific electrode within 15 minutes.

Results. In all patients levels of ionized calcium decreased from baseline during CPB. (Table 1) This reduction in ionized calcium was not related to previous treatment with calcium channel blockers or duration of CPB (p = ns). However, the lowest levels of ionized calcium were found in patients with the longest duration of CPB ($p>0.05$). In patients who received at least 10 mg/kg of calcium chloride, ionized calcium levels returned to pre CPB levels by the time of transfer to the ICU (2° after administration of calcium).

Patients with normal pulmonary vascular resistance experienced no deterioration in RV function (as assessed by RVEF and PAP). Administration of 10 mg/kg or more of calcium often resulted in a transient increase in both cardiac output and RVEF. Eight patients in our study had both elevated PVR and depressed RV function. The RV data from these patients are presented in Table 2. Administration of calcium chloride to these patients post CPB did not result in a significant increase in PVR or deterioration in RV function.

Discussion. The level of free ionized calcium decreased in all of our patients during CPB. In fact in those patients with CPB times greater than 2 hours, the levels were often below normal limits. It is because of this previously hypothesized decrease in ionized calcium during CPB and because of its positive ionotropic properties, that calcium is often administered empirically on separation from CPB. If, however, calcium administration also produced marked increase in PVR, then its administration might be deleterious in patients with already elevated PRV and depressed RV function. However, the results of our study failed to detect any detrimental effect on PVR following calcium chloride administration. In fact RV function was significantly augmented following calcium. Previous results from animal data reporting an elevation in PVR following calcium chloride were not supported by our study data. Even in surgical patients, with pulmonary vascular hypertension, calcium failed to result in further increases in PVR. Our data demonstrate no alternations in PVR following calcium chloride.

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TABLE I
IONIZED CALCIUM LEVELS IN PATIENTS
BEFORE AND AFTER CPB

	Baseline	Post CPB	After Calcium Chloride (mg/kg) 5	10	15	20
Ionized Ca Meq/L	4.83±.20*	4.32±.27*	4.72±.04	5.30±.40	5.32±.44	5.67±.19

Average ± S.D.
* $p < .05$

TABLE II EFFECT OF CALCIUM ON PATIENTS
WITH ELEVATED PVR[1]

	Pre CPB[2]			Post CPB			Post CPB after Calcium		
	PA[3]	PVR[4]	RVEF	PA	PVR	RVEF	PA	PVR	RVEF
Control (10)	15±5	56±24	57±10	16±6	63±39	60±10	17±4	64±37	58±11
Elevated PVR (7)	27±9	267±110	36±7	26±8	156±73	41±11	28±7	163±58	44±6

1. Mean ± SD
2. After sternotomy but prior to aortic cannulation
3. Mean pulmonary artery pressure (mmHg)
4. Pulmonary vascular resistance dynes/sec/cm^2
5. Patients received calcium chloride at 10 mg/kg IV

Title: INTERPLEURAL BUPIVACAINE IN THE DOG: DISTRIBUTION OF EFFECT AND INFLUENCE OF INJECTATE VOLUME

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Introduction. The injection of local anesthetic solutions into the interpleural (IP) space has been shown to be effective in postoperative pain management (1). Although direct proof in humans is lacking, it has been speculated that the analgesia occurs as a result of an intercostal (IC) and/or paravertebral sympathetic nerve block (2,3) or perhaps via a direct CNS action of the local anesthetic drug. Initial findings in dogs (4) have indicated a substantial presence of a gravity-influenced IC nerve block and no CNS effects following 10 ml of 0.5% bupivacaine (B) given IP. However, little or nothing is known of the effects of injectate dose and volume on the extent and distribution of the IC block following IP B or whether increasing the volume will involve CNS (e.g. spinal) structures as well. This issue was investigated in the present study employing a dog model for IP administration of B and evoked potential (EP) analysis.

Methods. Adult male mongrel dogs were used and the study protocol was IACUC approved. The animals were surgically prepared with chronic femoral arterial and venous catheters. Electrode pairs were attached (in relationship to the spine) to the proximal (P), middle (M) and distal (D) aspects of the right 5th, 7th and 9th ribs and to the ipsilateral laminae (L) of the corresponding thoracic vertebrae (T_5, T_7, T_9) (4). The electrodes were fixed in place with stainless steel screws and epoxy. The IP catheter was placed over the right 7th rib. Studies were initiated at >1 week following surgery. For study, the dogs were placed in a lateral position (right side down), anesthetized with 0.6% halothane/50% N_2O/50% O_2, paralyzed (pancuronium), and mechanically ventilated. Control IC nerve EPs were obtained over a 1-2 h period with stimuli (at 2-5 mA) applied at the D, M, and P loci of each rib and recordings taken from the appropriate L. In addition a spinal EP measurement was made with stimulus (2 mA) at the T_5 L and recording at the T_9 L. The animals were then injected with 10 ml of 0.5% B via the IP catheter. The EP measurements were repeated 40-90 min later. A second experiment using the above protocol was performed on the same animal 1 week later, with the exception that 20 ml of 0.5% B was injected.

Results. Our analysis of the effects of IP B on IC nerve or spinal transmission was based on measurements of the maximal peak-to-peak (positive to negative) amplitude of the recorded EP. As shown in the figure to the right, with all values expressed as a percentage of control, IP B did not produce a spinal block at either volume of injectate. On the other hand, IC nerve EP amplitudes were substantially attenuated. Thus, the magnitude of the nerve block was generally seen as $T_5 > T_7 > T_9$ with D>M>P in the T_5 and T_7 IC nerves. In 8 of 9 IC stimulus sites the 20 ml injection, resulted in a markedly greater effect than the 10 ml injection, with a complete block being observed at all loci in the T_5 IC nerve following 20 ml IP B. No complete blocks were seen following 10 ml. Furthermore, at 3 sites (T_7 P and T_9 D and M), where little or no effect on EP amplitude accompanied the 10 ml injection, a substantial attenuation occurred in the presence of 20 ml IP B.

Discussion. The present observation of greater levels of IC nerve block at more distal loci, with the dog in the right-side down position, agrees with a previous finding of gravity-dependent pooling of drug at or near the D site. With the dog lying on its side, the shape of the chest wall is similar to a saucer. Because of gravity, IP B will accumulate at the lowermost sites of this saucer. Our results are consistent with T_5 loci most dependent, T_7 loci intermediate, and T_9 loci least dependent in the cephalad-caudal axis. In the medial-lateral axis, D loci are most dependent, M loci intermediate, and P loci least dependent. Increasing the volume and dose of IP injectate results in greater EP attenuation of sites blocked by the smaller dose. Additionally, there is a greater distribution of EP attenuation with increased volume and dose, as evidenced by blockade of sites not affected by the smaller dose.

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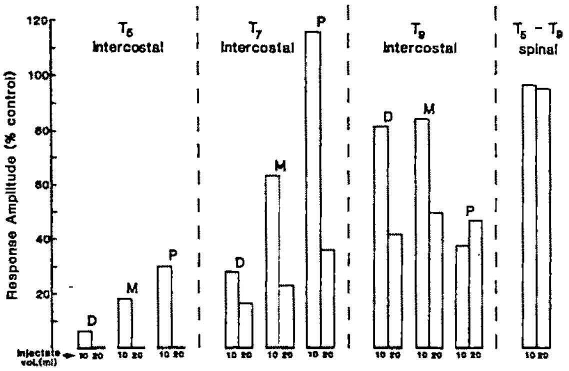

Fig. 1. EP amplitude changes following IP bupivacaine. See text for definition of symbols.

TITLE: DEXTROMEDETOMIDINE, ACTING VIA CENTRAL ALPHA-2 ADRENORECEPTORS, PREVENTS ALFENTANIL-INDUCED MUSCLE RIGIDITY IN THE RAT.

Authors: M. B. Weinger, M. D.*, I. S. Segal M.D.# and M. M. Maze, M. B.#
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Introduction. Recent work has identified the highly-selective alpha-2 adrenergic agonist, dextromedetomidine (d-MED) as a potentially useful anesthetic agent [1]. Dextromedetomidine decreased halothane MAC by up to 100% and also decreased sympathetic activity in a dose-dependent manner. In pilot studies we have also noted that d-MED is a potent analgesic and produces flaccidity. These properties may make d-MED an ideal adjuvant to high-dose opiate anesthesia. Because muscle rigidity is an undesirable side-effect of potent short-acting opiate agonists, the d-MED could be therapeutic by producing flaccidity. While the neurochemical mediators of opiate-induced rigidity have yet to be fully elucidated, recent work suggests an adrenergic component [2]. The present study was designed to evaluate the effects of pretreatment with dextromedetomidine on alfentanil-induced muscle rigidity in the rat.

Methods. Following Animal Care Committee approval, 33 male Wistar rats (220-260 kg) were randomly assigned to one of 5 treatment groups. The animals were placed in cages and muscle rigidity was measured as described previously by electromyographic (EMG) recordings from the left gastrocnemius muscle [3]. After 15 minutes of baseline measurements, the rats were injected (1 ml/kg i.p.) by a "blinded" observer with either Levomede- tomidine (the inactive L-isomer of medetomidine), 30 µg/kg, (n=7), d-MED, 10 µg/kg (n=7), d-MED, 30 µg/kg (n=8), the combination of d-MED, 30 µg/kg, and the central-acting alpha-2 antagonist, idazoxan, 10 mg/kg (n=7), or the combination of d-MED, 30 µg/kg, and the hydrophilic peripheral-acting alpha-2 antagonist DG5728, 10 mg/kg (n=6) [see **Table**]. Fifteen minutes after pretreatment, all rats received alfentanil [ALF] (0.5 mg/kg s.c.) and EMG data were collected every 5 minutes for 60 minutes. The total area under the EMG activity versus time curve was calculated as a measure of degree of ALF rigidity [Table]. Data were analyzed using ANOVA followed by Newman-Keuls tests with a P value of 0.05 considered significant.

Results. There were no differences between groups with respect to weight or baseline EMG activity. None of the pretreatment regimens produced a significant alteration in baseline EMG activity although the group receiving the 30 µg/kg dose of d-MED alone appeared more flaccid and reacted less to the subsequent subcutaneous injection. One animal in the d-MED/DG5728 group died precipitously shortly after receiving the ALF injection.

ALF resulted in a marked increase in hindlimb EMG activity in the group treated with the inactive isomer, levomedetomidine (**Figure**). In contrast, d-MED 30 µg/kg prevented ALF-induced muscle rigidity [P<0.01] (**figure**). The d-MED (30 µg/kg) animals were flaccid, akinetic, and lacked a startle response during the entire 60 minute experimental period. The lower d-MED dose (10 µg/kg) produced no measurable effect. At the end of the 90-min experiment, the d-MED rats had a slow but intact righting reflex despite persistent flaccidity. The addition of the central alpha-2 antagonist, idazoxan, eliminated d-MED's blockade of ALF-induced muscle rigidity. In contrast, DG5728 failed to appreciably reverse d-MED's antagonism of ALF rigidity; although there was a slight but significant increase in muscle activity after ALF in the DG5728 with d-MED compared with the group receiving d-MED (30 µg/kg) alone.

Table.

Pretreatment Regimen	n	Rigidity after ALF (Mean ± SEM)	
1. Levomedetomidine (30 µg/kg) (control)	7	257 ± 45	
2. Dextromedetomidine (10 µg/kg)	7	247 ± 37	
3. Dextromedetomidine (30 µg/kg)	8	43 ± 8	*
4. d-MED (30)+DG5728 (10 mg/kg)	5	106 ± 20	*
5. d-MED (30)+idazoxan (10 mg/kg)	7	331 ± 45	

* $P<0.05$ compared with all other groups.

Discussion. The results of this study clearly demonstrate that pretreatment with dextromedetomidine prevents opiate-induced muscle rigidity in the rat. Complete reversal of this effect by the central antagonist idazoxan but only slight reversal by the peripheral antagonist DG5728 suggests that dextromedetomidine is acting *via* central alpha-2 adrenoreceptors. The d-MED dose sufficient to antagonize ALF rigidity is the IC$_{50}$ for its halothane MAC-reducing effect [4]. The precise relationship between d-MED's activation of central alpha-2 receptors and the reversal of opiate rigidity must still be determined. Profound flaccidity seen in the d-MED-treated animals implies that a combination of opiates and a selective alpha-2 agonist such as dextromedetomidine might produce anesthetic conditions and surgical relaxation with a significantly reduced need for neuromuscular blocking agents.

In conclusion, our results suggest that small doses of the highly selective alpha-2 agonist dextromedetomidine may be clinically effective in preventing the muscle rigidity caused by high-dose opiates. This effect appears to be due to the activation of central alpha-2 adrenoreceptors. Dextromedetomidine may also produce other clinically-desirable effects such as analgesia and skeletal muscle relaxation.

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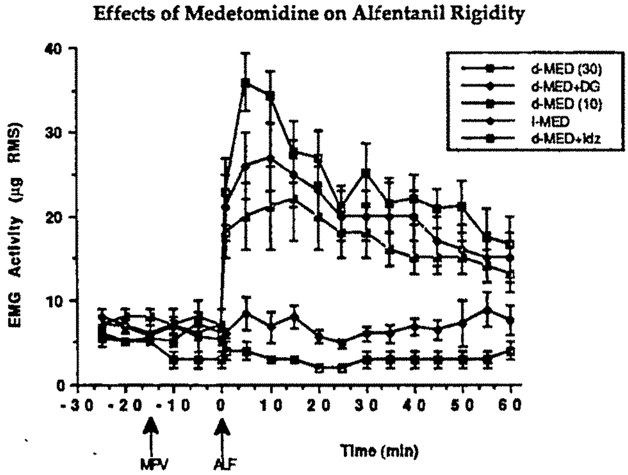
Alfentanil was generously provided by Janssen Pharmaceutica. Stereoisomers of medetomidine were generously provided by Farmos Pharmaceutica. Dr.Weinger is a Parker B. Francis Investigator in Anesthesiology.

Figure.



Title: **CARDIOVASCULAR SAFETY AND ACTIONS OF HIGH CONCENTRATIONS OF I653 AND ISOFLURANE IN SWINE**

Authors: Richard B. Weiskopf, M.D., Margot A. Holmes, A.B., Edmond I. Eger, II, M.D., Brynte H. Johnson, M.S., Nobuhiko Yasuda, M.D., Alexander G. Targ, B.S., Ira J. Rampil, M.D.
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Introduction: Concentrations from 0.8 to 1.6 MAC of I653 (CF_2H-O-CFH-CF_3), a new inhaled anesthetic, produce cardiovascular (1) and electroencephalographic (2) actions similar to those of isoflurane. In this study, we determined the ratio of concentration of I653 and of isoflurane at cardiovascular collapse to their minimum alveolar anesthetic concentration (MAC). To identify physiologic changes that indicate the approach of a dangerously high anesthetic concentration, we also measured some cardiovascular and metabolic actions of relatively high concentrations of these anesthetics.

Methods: This study was approved by the UCSF Committee on Animal Research. We placed indwelling aortic and thermodilution pulmonary arterial cannulae in eleven young (age 11-15 weeks; weight 20.7 ± 1.4 kg, mean ± S.E.) female domestic swine. Animals were studied at least 7 days after surgery, at which time all were in good health. Anesthesia was induced with I653 (6 swine) or isoflurane (5 swine; choice randomly assigned) in oxygen, via a mask. Body temperature was maintained within 0.5 C° of the awake value. Animals' lungs were ventilated to maintain normocapnia. Initial measurements were made after 15 min of a stable end-tidal anesthetic concentration of 1.1-1.2 MAC. Anesthetic concentration was then increased by 0.35 - 0.4 MAC, and after 15 minutes of stable end-tidal concentration, measurements were repeated. This process was repeated until the animal died. For each anesthetic, data and computed values were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons. Data and computed values at appoximately equipotent anesthetic concentrations, and the ratio of anesthetic concentration at death to the MAC determined in each pig were compared between I653 and isoflurane by Students unpaired t-test. Statistical significance was accepted at $P < 0.05$.

Results: I653 and isoflurane produced closely parallel curves defining survival as a function of anesthetic concentration, with a constant separation throughout of approximately of 1/2 MAC (Fig. 1). For the six swine given I653, MAC was 9.8 ± 0.3%, the fatal concentration was 23.9 ± 0.06%, and the ratio of fatal concentration to MAC was 2.45 ± 0.11. For isoflurane these values were 2.07 ± 0.08%, 6.22 ± 0.23%, and 3.02 ± 0.13 ($P<0.05$), respectively. Over the entire range studied, cardiac output (Q_t) and arterial blood (MAP) pressure decreased as a linear function of anesthetic concentration (Fig. 2), while heart rate (HR) did not change. Above 1.4 - 1.6 MAC Q_t and MAP were higher in swine anesthetized with isoflurane than in those given I653. HR did not differ between the two anesthetics. Blood lactate concentration and base-deficit did not change with either anesthetic. Below concentrations of 2.0 MAC I653 or 2.4 MAC isoflurane, mixed venous oxyhemoglobin saturation (S_vO_2), mixed venous PO_2 (P_vO_2)(Fig.2), and the ratio of oxygen transport to oxygen consumption (TO_2/VO_2) equalled or exceeded values in conscious swine(1). Higher anesthetic concentrations sharply decreased values for these variables ($P < 0.05$). Values for these variables lower than those in conscious swine heralded cardiovascular deterioration and death at the next higher anesthetic concentration. At anesthetic concentrations approaching and causing cardiovascular collapse in each animal, P_vO_2, S_vO_2, and TO_2/VO_2 did not differ between I653 and isoflurane.

Discussion: The margin of safety for I653 lies between that for isoflurane and those reported for other halogenated anesthetics (3,4,5). The fatal-to-anesthetic ratio for I653 is 81% of that of isoflurane, while the ratios for enflurane, methoxyflurane, and halothane are 58%, 65%, and 53% of that determined for isoflurane. Since cardiovascular collapse occurs at a higher anesthetic concentration than does apnea, during spontaneous ventilation alveolar concentrations of I653 capable of causing cardiovascular collapse usually can not be attained. During controlled ventilation, P_vO_2, S_vO_2 and TO_2/VO_2 were the variables which changed most noticeably as anesthetic concentration approached the fatal level. These variables appear to be the best indices of excessive anesthetic concentration.

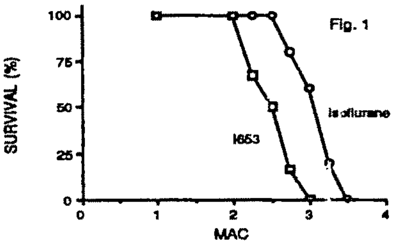
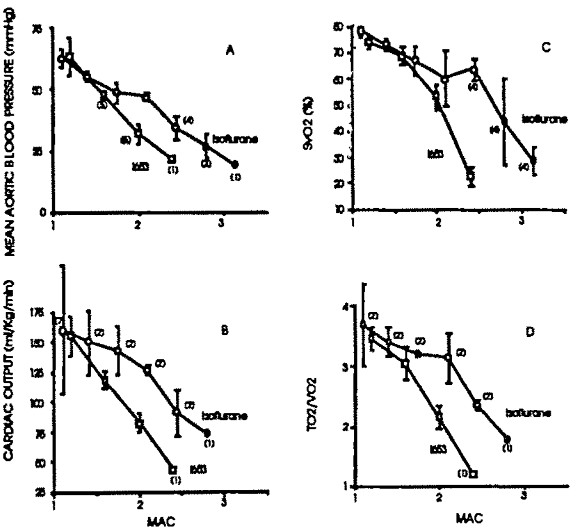


Figure 2



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Title: ATROPINE AND GLYCOPYRROLATE DO NOT INHIBIT THE EFFECTIVENESS OF METOCLOPRAMIDE AND CIMETIDINE IN THE GENERAL SURGICAL POPULATION

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Introduction: Metoclopramide, a dopamine agonist with proven gastrokinetic effects (1), and cimetidine, a selective and competitive H2 receptor antagonist, have been recommended prior to general anesthesia (GA) (2,3,4) for prevention of the acid aspiration syndrome in both non-obese and morbidly obese patients. Some investigations have suggested that atropine may inhibit the gastrokinetic effects of metoclopramide (4,5,6). The goal of this study was to determine if there is a clinically significant inhibition of the metoclopramide(M) - cimetidine(C) regimen by atropine(A) or glycopyrrolate(G).

Methods: 36 ASA physical status I through III patients scheduled for elective surgical procedures under GA gave their informed consent for this institutional review board approved placebo controlled study. Patients were excluded for any of the following reasons: morbid obesity(100 lbs > ideal body weight), active GE reflux, age < 18 or > 65, concurrent use of C or M. All patients had fasted a minimum of 7.5 hours, and were randomly assigned to one of 4 groups:

GROUP	TREATMENT
A	Placebo at hs; Placebo on call to OR
B	C at hs; C and M on call to OR
C	C at hs; C, M and A on call to OR
D	C at hs; C, M and G on call to OR

* Dose C=300 mg, M=20 mg, A=.4 mg IM, G=.2 mg. All given p.o. with 30 ml H_2O.

Anesthesia was induced intravenously, with choice of agents at the discretion of the staff anesthesiologist. After induction and intubation, an 18 Fr gastric tube was inserted orally and its position confirmed by auscultation; stomach contents were then aspirated with a catheter-tipped syringe. The gastric volume was measured, and pH determined with a Beckman Expandomatic pH Analyzer and calomel combination electrode. One of the authors, blinded to patient group, obtained and analyzed the samples.

Differences among the groups for age, weight, height, time interval from medication, pH and volume were analyzed by analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant. Results are expressed as mean ± S.D.

Results: There were no differences among the groups for age, weight, height, or time interval from medication. Patients in the placebo group had a significantly lower pH and higher gastric volume than groups B, C, and D. There were no statistically significant differences among Groups B, C, and D (Table I).

Table I. Results by Group

GP	n	pH	Volume	% with pH ≤ 2.5*	% with Vol ≥ 25 cc	% pH < 2.5 vol ≥ 25 cc
A	8	2.87±2.41	50.1±38.4	75	50	38
B	10	6.22±1.74	15.6±12.2	0	20	0
C	7	4.97±2.26	18.3±23.4	20+	29	14
D	11	5.74±2.61	22.2±27.1	20‡	18	9

+2 patients with 0 volume excluded; ‡1 patient with 0 volume excluded.

Discussion: We previously showed that atropine has an inhibitory effect on metoclopramide in the morbidly obese surgical population.[3] The current study failed to show statistically or clinically significant inhibition of metoclopramide by atropine or glycopyrrolate.

We postulate that the inhibitory effect of atropine on metoclopramide may be more apparent in the morbidly obese secondary to their higher resting gastric volume and decreased gastric motility. For these reasons the gastrokinetic effect of metoclopramide on these patients would be more pronounced than in non-morbidly obese patients with normal gastric motility. Our population was similar to previous studies in that 38% of our placebo group was "at risk" for pulmonary aspiration (pH ≤ 2.5, Vol ≥ 25 ml) In conclusion, addition of atropine or glycopyrrolate to the metoclopramide-cimetidine prophylactic regimen does not decrease its efficacy in non-obese patients.

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Flow-Volume Relations During Spontaneous Breathing Through Endotracheal Tubes

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Introduction. In the operating room and intensive care unit, patients frequently breathe spontaneously through a endotracheal tube (ET). It is often said that breathing through an ET is "like breathing through a straw." Endotracheal tubes cause airflow resistance inversely proportional to their diameter (1). Studies in normal subjects using tubular resistors to simulate ET reveal substantial alterations in breathing patterns (2). Little has been done to determine whether ET's functionally act as tubular resistors in intubated patients especially since such patients frequently have small tidal volumes and reduced vital capacities. This study examines endotracheal flow-volume relationships to determine if there is evidence of airway obstruction during tidal breathing.

Methods. Eighteen mechanically ventilated, critically ill postoperative (abdominal and thoracic procedures) patients with 7mm (N=5) and 8mm (N=13) endotracheal tubes breathing spontaneously while on intermittent mandatory ventilation (IMV) were studied. Flow-volume relationship were measured during both mechanical and spontaneous breathing with the patients in the semi erect position. Ten of the patients were also studied during forced vital capacity (VC) maneuvers. A Horizon 4400 pulmonary function testing instrument (Sensormedics, Anaheim CA) was used to perform the measurements. Its turbine flow measurement device was calibrated at 0.5L and validated at 1L. The inspiratory phase of the mechanical breaths were not analyzed since the Bear ventilators generate square waveflow patterns. To determine if flow limitation exists, visual inspection of the curves and the ratios of forced expiratory volume in 1sec to that in 0.5sec ($FEV_1/FEV_{0.5}$) and peak expiratory flow rate to FEV_1 ($PEFR/FEV_1$) ratios were examined. Rotman (3) reported that upper airway obstruction $FEV_1/PEFR > 10$ml/L/min and $FEV_1/FEV_{0.5} > 1.5$. This study was approved by the Columbia University IRB.

Results. The composite expiratory flow-volume curves for 72 spontaneous and 72 machine breaths (in 18 patients) as well as 20 vital capacity measurements (in 10 patients) are displayed in Figure 1.

Peak Inspiratory (PIFR) and Expiratory (PEFR) Flow Rates (mean ± SD)

	PIFR (l/S)	PEFR (l/S)	$FEV_1/FEV_{0.5}$	$PEFR/FEV_1$ (ml/L/min)
Spont	0.84 ± 0.1	0.84 ± 0.2	1.5 ± 0.6	6.6 ± 0.6
VC	1.0 ± 0.3	1.0 ± 0.3	1.7 ± 0.1	12.9 ± 1.2
Machine		1.0 ± 0.4	1.7 ± 0.1	10.8 ± 1.5

Discussion. Flow volume loops are used to diagnose fixed and variable intra and extrathoracic airway obstruction. Depending on the type and site of the obstruction, different patterns of flow limitation are produced. Endotracheal tubes can act as fixed obstructions as demonstrated by the flow-volume patterns produced by two patients (not postoperative) with vital capacities greater than 2.5 liters and intubated with 6mm ET (Fig. 2&3). However, the postoperative patients studied were intubated with larger diameter (7 or 8mm) ET and had markedly reduced vital capacities. Visual inspection of their expiratory flow- volume curves failed to reveal any evidence of flow limitation (flattening of the curve) during spontaneous and machine breaths. Minimal flattening of the curve was noted during vital capacity maneuvers. Examination of $FEV_1/PEFR$ and $FEV_1/FEV_{0.5}$ revealed some degree of obstruction during VC and machine but not spontaneous breathing. The PIFR:PEFR ratio was 1.0 indicating either poor effort (due to pain on forced expiration) or fixed flow limitation. The evidence of some obstruction is consistent with the findings of Empy (3) who found minimal elevation in $FEV_1/PEFR$ in normal subjects breathing through a mouthpiece fitted with an 8mm orifice. These normal subjects had PEFR's 5-6 times those of the postoperative patients.

In conclusion, the small tidal volumes, reduced vital capacities, slow flow rates and relatively large diameter ET resulted in only a small degree of functional fixed upper airway obstruction during flow-volume measurements in postoperative patients. Much of the discomfort and work during spontaneous breathing through endotracheal tubes may be caused by the isovolemic pressure maneuvers needed to overcome threshhold resistors such as demand values.

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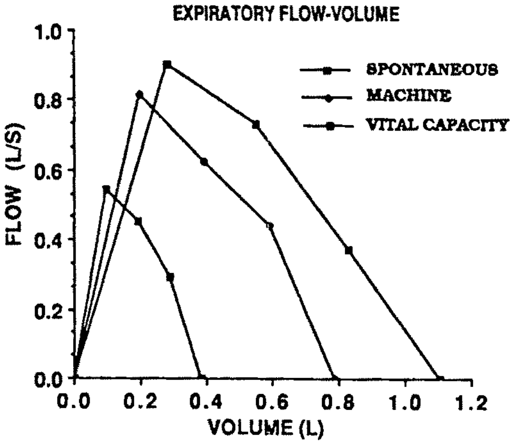

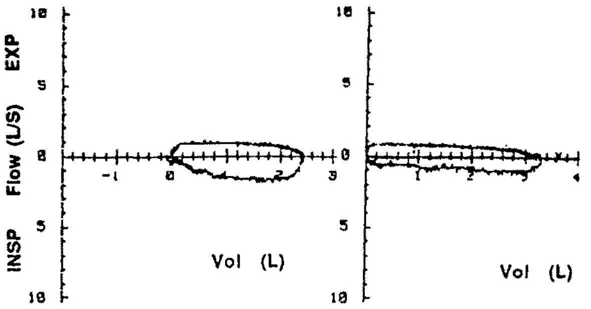

Title: LOWER ESOPHAGEAL CONTRACTILITY CAN BE USED TO CONTROL ALFENTANIL INFUSIONS

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Introduction. Recent studies have described methods for the continuous infusion of narcotics in combination with nitrous oxide.[1-3] By definition, any parameter which can be used to reliably control the delivery of anesthetic agents is a measure of anesthetic depth. Lower esophageal contractility (LEC) has been reported to be a measure of anesthetic depth.[4,5] The present study tested the hypothesis that LEC could be used as the sole criterion for determining the rates of continuous alfentanil infusions during alfentanil/nitrous oxide anesthesia.

Methods. With Investigational Review Board approval, we studied eleven ASA I and II patients aged 34–66 years scheduled for lower abdominal gynecologic surgery of 45 min – 3 hr duration. Patients were premedicated with midazolam 2–5 mg IV. Following a 20 mcg/kg alfentanil bolus, anesthesia was induced with sodium thiopental 3–5 mg/kg. Succinylcholine 1 mg/kg was used to facilitate endotracheal intubation, and muscle relaxation was accomplished with either vercuronium or pancuronium. Ventilation was controlled to maintain $P_{ET}CO_2$ at 35 ± 3 mm Hg. Anesthesia was maintained with N_2O 70% and a continuous alfentanil infusion initially set at 1.0 mcg/kg/min.

Beginning five minutes post incision, the alfentanil infusion rate was varied according to the following criteria: If the esophageal contractility index (ECI)[4] was less than 30 for nine minutes, the infusion rate was decreased by 0.25 mcg/kg/min; if the ECI was greater than 120 for six minutes, a 7.5 mcg/kg alfentanil bolus was administered and the infusion rate was increased by 0.25 mcg/kg/min. If heart rate (HR) exceeded 100 bpm and/or if systolic blood pressure (SBP) exceeded 160 mm Hg, the investigator was allowed to intervene with appropriate administrations of alfentanil, calcium channel or beta-adrenergic blockers, or an inhalational anesthetic agent. The alfentanil infusion was discontinued 15 min prior to the anticipated end of surgery.

SBP (via oscillotonometry), HR (via ECG lead II), ECI, and alfentanil infusion rates were recorded every three minutes. Alfentanil was administered with a Model 900 Harvard Mini Infuser (Bard). LEC was measured using the Lectron 302 monitor and probe (American Antec). The probe is equipped with two balloons: an air-inflatable balloon for provoking esophageal contractions and a liquid-filled balloon (connected to a pressure transducer) for measuring all contractions.

Results. For all 11 patients, ECI was the only parameter used to control the alfentanil infusion rate. SBP exceeded 160 mm Hg once in two patients, and one patient's HR exceeded 100 bpm for one measurement episode. All three patients received nifedipine 10 mg intranasal and did not require further treatment. The remaining eight patients did not require any therapeutic interventions.

The average length of surgery was 87 ± 42 (SD) min, and the mean alfentanil dose was 111 ± 34 mcg/kg. Times from reversal of muscle relaxation to spontaneous respiration and eye opening were 2.5 ± 1.8 min and 4.7 ± 1.6 min, respectively. No narcotic antagonist was required or used. Upon postoperative follow-up, no patients reported awareness during the operation.

Discussion. The pharmacokinetic properties of alfentanil allow for its continuous infusion in combination with nitrous oxide to produce satisfactory general anesthesia. Previous studies have controlled the infusion rate by observing patient signs (somatic, hemodynamic, and sympathetic) of inadequate anesthesia.[1,3] The purpose of this study was to develop a more sensitive and reliable control technique which could help avoid the problems associated with "too deep" or "too light" anesthesia.

The three patients in this study with elevated hemodynamics were treated with a vasoactive rather than an anesthetic agent. Because the ECI was less than 120 (and, hence, the patients were thought to be adequately anesthetized) it was deemed appropriate to treat the hemodynamic changes with a vasoactive agent.

This study revealed that LEC can be used to control the rate of continuous alfentanil infusions. Additionally, LEC can aid in determining appropriate intervention therapy for hemodynamic control. Thus, LEC appears to be a useful indicator of anesthetic depth during alfentanil/nitrous oxide anesthesia.

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DOSE-DEPENDENT BLOOD FLOW VELOCITY CHANGES IN THE BASAL CEREBRAL ARTERIES FOLLOWING LOW-DOSE KETAMINE

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INTRODUCTION: The central nervous system is the main site of action for anesthetics. Electrophysiological monitoring allows noninvasive assessment of the cerebral functional integrity but it can only serve as an indirect indicator for the adequacy of cerebral blood flow (CBF). Noninvasive transcranial Doppler sonography (TCD) measuring cerebral blood flow velocity (BFV) provides information on cerebral hemodynamics. The present study was performed to evaluate the role of TCD as a new possible method in cerebral monitoring following application of anesthetics by comparing the effects of 0.25mg/kg versus 0.5mg/kg (bodyweigth) intravenous ketamine on BFV in the basal cerebral arteries.

METHODS: Written informed consent and the approval of the Clinical Research Ethics Committee was obtained in 20 healthy volunteers, randomly assigned to group A (m=7,f=3, 0.25mg/kg ketamine i.v.) and group B (m=5,f=5, 0.5mg/kg ketamine i.v.). Mean arterial blood pressure (MAP, Dinamap™), heart rate (HR), end-tidal CO2 (PetCO2, Datex™) and oxygen saturation (SaO2, Nellcor™) were measured over a period of 70 minutes. BFV were monitored by transtemporal approach for the proximal stem of the middle cerebral artery (MCA) with a pulsed 2MHz Doppler ultrasound system (TC2-64B, EME™). This Doppler device is constructed with a range-gating mechanism allowing sample volume movements in 5mm steps, flow direction discrimination and real-time monitoring of the flow velocity profile after spectral analysis (FFT) averaging cycles of 4 seconds. Systolic and mean flow velocity (Vsyst/mean) as well as the pulsatility index (PI=Vsyst-Vdiast/Vmean) are calculated automatically. Data were subjected to analysis of variance (ANOVA) and Friedman-test for repeated measurements where appropriate ($p<0.05$).

RESULTS: Dose-dependent increases in systemic hemodynamic parameters and BFV in the MCA were noted in both groups for different time periods. Changes in Vmean were more marked compared to changes in MAP as indicated by different significance levels (cf. Table/Figure). PI decreased simultaneously to the BFV-changes while no significant differences could be documented for PetCO2 and SaO2.

	HR (1/min)		MAP (mmHg)		Vmean (cm/sec)	
group	A	B	A	B	A	B
t 0	73± 16	62± 17	88± 9	91± 12	56± 8	68± 14
(min.)1	88± 12 *	85± 22 *	95± 9	99± 11	59± 10	88± 25 *
2	93± 17 *	90± 21 *	104± 8 *§	112± 9 *	65± 11 *$	108± 30 *
3	95± 23 *	94± 20 *	106± 7 *§	117± 10 *	70± 12 *$	116± 29 *
4	103± 28 *	91± 20 *	107± 8 *§	120± 13 *	72± 16 *$	119± 33 *
5	96± 25 *	97± 21 *	105± 10 *§	118± 10 *	68± 11 *$	114± 31 *
7	87± 20 *	93± 16 *	98± 7 *§	118± 14 *	64± 8 $	104± 30 *
10	76± 8	82± 11 *	96± 9	108± 9 *	61± 10 §	86± 23
20	74± 12	73± 13 *	93± 9	103± 10 *	59± 10	80± 18
30	71± 12	72± 12 *	91± 7	98± 8	57± 12	77± 17

Tab.: Heart rate (HR), mean arterial blood pressure (MAP) and mean blood flow velocity (Vmean) in the MCA after 0.25mg/kg (group A) vs. 0.5 mg/kg (group B) ketamine; (mean+SD); *-significant vs control (time 0 min.); § -significant vs group B ($p<0.05$); $-significant vs group B($p<0.01$)

DISCUSSION: Under varying conditions as changes in MAP, PetCO2 or during sensory evoked changes in blood flow the diameter of the basal cerebral arteries can be assumed to remain constant (2,3). Changes of flow velocity would therefore provide information on relative changes in CBF. The significant dose-related increases in all hemodynamic parameters following administration of 0.25 or 0.5mg/kg ketamine intravenously, which is supposed to increase CBF (1), correlate well with increases in the flow velocity profile obtained by TCD. The decrease of PI suggests a decrease in cerebral vascular resistance (4). In the present study PetCO2 and SaO2 remained within their respective physiologic ranges, which allows to exclude a major influence on cerebral hemodynamic changes. With respect to technical limitations of Doppler ultrasonic methods the results may indicate a dose-related decrease of cerebrovascular resistance resulting in a ketamine - induced increase of CBF. The differences in Vmean between group A and B cannot be explained by differences in HR or MAP. TCD seems to be a suitable method in detecting cerebral hemodynamic changes induced by ketamine. Further investigations on the correlation between flow velocity changes and CBF will be necessary to validate TCD - signals as an appropriate parameter for the detection of inadequate cerebral perfusion during anesthesia.

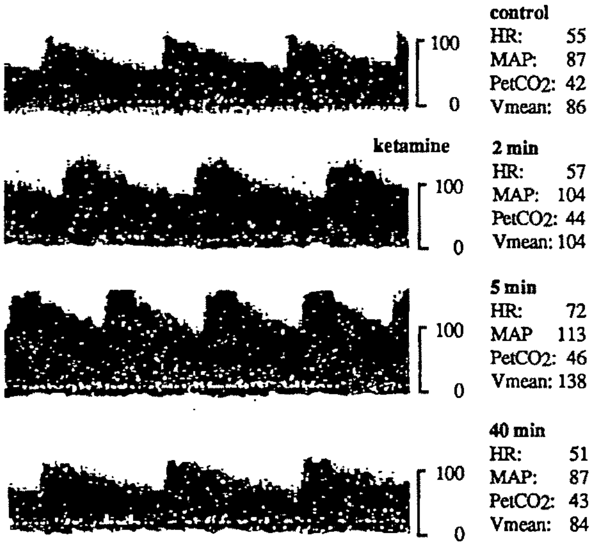

Fig.: Changes of flow velocity, heart rate {HR: (1/min)}; mean arterial pressure {MAP: (mmHg)}; endtidal CO2 {PetCO2 (mmHg)}; and mean blood flow velocity in the MCA {Vmean (cm/sec)} following ketamine (0.5 mg/kg)

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TRANSCRANIAL DOPPLER SONOGRAPHY AS A SUPPLEMENT IN THE DETECTION OF CEREBRAL CIRCULATORY ARREST

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Introduction: Cerebral circulatory arrest is accepted as one specific criterion in the determination of brain death (1, 2). In addition to standardized neurological examination, neurophysiological techniques like recordings of EEG and evoked potentials as well as extracranial Doppler ultrasound have been applied for diagnosis of brain death. This study was performed to present transcranial Doppler sonography (TCD) as a supplementary noninvasive diagnostic bedside method for the detection of developing pathological cerebral hemodynamics and the determination of cerebral circulatory arrest by direct insonation of the basal cerebral arteries.

Methods: 10 mechanically ventilated head injured patients, already diagnosed as brain-dead and prepared for organ donation and one mechanically ventilated patient after cardiopulmonary resuscitation (m=6, f=5; age 21-43) were included in the study. Diagnosis was based on neurologic examinations and EEG-recordings. Cerebral circulatory arrest was studied with a pulsed 2 MHz bidirectional Doppler ultrasonographical system (TC2-64B, EME™) by transtemporal approach for the anterior (ACA) and middle cerebral artery (MCA). Systemic invasive arterial blood pressure and heart rate were monitored and blood gas analysis was performed. Body temperature was measured via a rectal or deep esophageal probe.

Results: Reliable TCD-signals could be obtained in all cases for the proximal stem of the MCA, whereas the ACA could only be insonated in 5 cases. The systolic flow velocity profile was markedly reduced (95-97% reduction) in comparison to normal flow velocity tracings (Fig. A) and revealed blood pressure- and ventilation-dependent amplitudes. The diastolic flow component consisted of retrograde phases (Fig.C). In the reanimated patient, normal flow velocities in the MCA could be obtained 2 hours after cardiopulmonary resuscitation followed by extremely increased blood flow velocities 24 hours following resuscitation (Fig.A), paralleled by excessive arterial hypertension (Fig.B). 36 hours after reestablished systemic circulation the typical TCD-signals indicated cerebral circulatory arrest (Fig.C), which was confirmed by neurological examination and EEG recordings. In all other patients the hemodynamic parameters and the blood gas tensions remained within their physiologic range with the exception of body temperature which was decreased to values between 30.8 °C and 33.4 °C.

Discussion: Cerebral circulatory arrest was indicated by the reverberating flow pattern with counterbalancing forward and backward movements of the blood column as a result of increased intracranial pressure. The reflex phenomenon during late systole and early diastole was found to be characteristic in all patients and is considered to be essential for the diagnosis of brain death (3). The interindividual variability of the systolic amplitudes may be explained by differences in cerebrovascular compliance, blood pressure and cardiac output. The pathological increase in the flow velocity demonstrated in Fig. B is interpreted as an uncoupled cerebral autoregulation with consecutive pressure - passive cerebral perfusion due to hypoxic cerebral damage but vasospasm of the MCA may be another explanation for the flow acceleration. Accurate examination has to involve all major basal cerebral arteries but lack of signals does not necessarily indicate impaired cerebral blood flow (CBF). TCD as a noninvasive method assessing the basal cerebral arteries seems to be suitable in detecting cerebral circulatory arrest as a supplementary diagnostic tool for brain death determination. It may also be useful in obtaining early changes in cerebral hemodynamics such as impaired autoregulation or CO2-reagibility in patients with severe brain lesions before brain death is established, which may be of importance with respect to transplantation programs. Further investigations have to validate the potentiality of TCD as a method in the detection of relative CBF-changes.

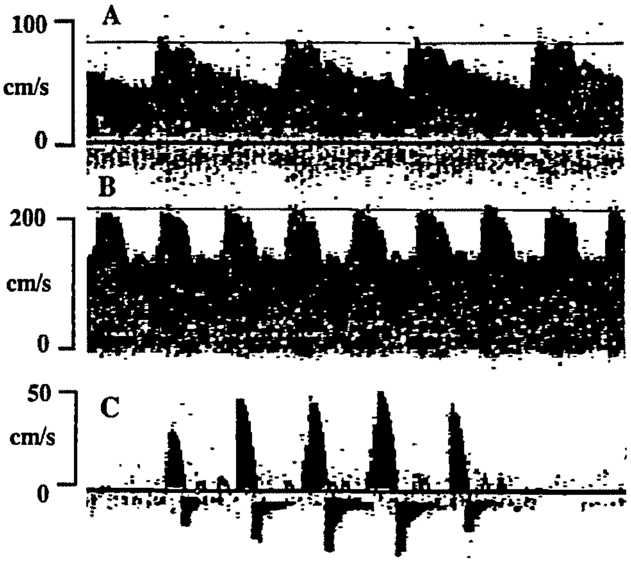

Fig.A: Normal MCA flow profile in a mechanically ventilated patient with a high diastolic flow velocity (V) towards the probe (Vmean: 56cm/sec)
Fig.B: Excessively increased MCA blood flow velocities in the same subject 22 hours later (Vmean = 138 cm/sec)
Fig.C: Low systolic flow velocity signals followed by early diastolic reversal of flow direction in the same patient as an indicator of cerebral circulatory arrest 34 hours later.
Note the different scales for blood flow velocity in the figures.

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Title: THE EFFECT OF INTRAVENOUS BOLUS POTASSIUM THERAPY

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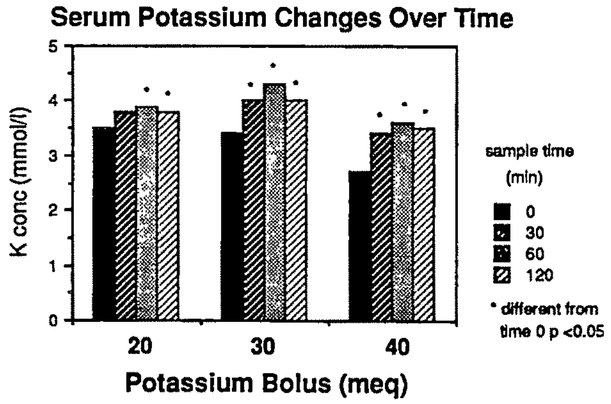
The safety and efficacy of an intravenous potassium (K^+) bolus infusion remains poorly understood, although thousands of such treatments are given each year in North America alone. We therefore investigated the serum K^+ levels before, during and after a 1 hour infusion of 20 mEq, 30 mEq or 40 mEq of KCl added in 100 cc of normal saline.

METHOD

Intravenous infusions of KCl in 100ml normal saline were infused through a central line over 1 hour. Twenty-six patients received 20 mEq, 11 received 30 mEq, and 11 others 40 mEq. Blood for serum K^+ level was drawn at 0 time, 30 minutes into the infusion, at the end of the infusion (60 minutes) and 1 hour later (120 minutes). All patients had venous blood samples drawn for creatinine, glucose, and magnesium, as well as arterial pH prior to therapy. All patients were in an ICU where each was monitored with an arterial line, ECG, a urinary catheter and a CVP line. The dose of KCl was selected on clinical grounds by the attending physicians. Patients who received 20 mEq had base-line serum K^+ levels between 2.9 and 4.3 mEq/1, those who received 30 mEq had base-line levels between 2.9 and 4.1 mEq/1, and those who received 40 mEq started between 2.1 and 3.1 mEq/1. This study was approved by the Human Ethics Committee of the University of Western Ontario.

RESULTS



All the patients showed a significant rise in serum K^+ over base-line at the end of the first 30 minutes of the infusion (except in the 20 mEq group, which became significant at 60 and 120 minutes). The serum K^+ remained significantly elevated over base-line at the end of the infusion and 1 hour thereafter. There was no significant change between the 30, 60 and the 120 minute levels at any dosage.

Table 1: MEAN AND RANGE OF THE MAXIMUM INCREASE IN SERUM POTASSIUM (ΔK^+ MAX)

DOSE (mEq)	ΔK^+ MAX (mEq/1) MEAN±SD		RANGE
20	0.47±0.27	> $p<.05$	0.1 - 1.2 mEq/1
30	0.92±0.41	> NS	0.4 - 1.6 mEq/1
40	1.07±0.4		0.4 - 1.6 mEq/1

Eleven patients had elevated serum creatinine ranging from 213-488 mmol/l, 6 in the 20 mEq group, 3 in the 30 mEq group and 2 in the 40 mEq group. The average and range of maximum increase in serum K^+ was actually less in these patients than in those patients with normal renal function.

There was no significant difference between the three dosage groups for blood glucose, pH and magnesium, nor was there any correlation between those variables and the change in serum K^+. As well, there was no correlation between the initial serum K^+, and the eventual maximum rise in serum K^+. No clinically significant changes occurred in the ECG or blood pressure during the study.

CONCLUSIONS

1. Intravenous infusion boluses of KCl over 1 hour produce a variable but significant increase in serum potassium, greater with 30 or 40 mEq than with 20 mEq.
2. Such boluses are clinically safe when administered to patients with base-line serum K^+ levels in the ranges noted, producing predictable levels with no hemodynamic instability.
3. After 30 minutes of the infusion, it appears that the serum potassium is the same as it is 1 hour after the infusion is completed. This may allow the clinician to predict future potassium levels and possible additional therapy.

Title: SPINAL ANESTHESIA SPARES DRUG METABOLISM IN THE DOG

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Introduction: It is now well recognized that anesthetic agents cause profound changes in perioperative drug disposition. Previous studies have shown that both volatile anesthetics (halothane, isoflurane, enflurane), and intravenous agents (fentanyl and propofol) inhibit drug metabolism. In addition, changes in hepatic blood flow induced by anesthetic agents and techniques may contribute to altered drug clearance during anesthesia, and thus the objective of the present study was to determine the effect of spinal anesthesia on drug disposition in the dog using propranolol as a model compound.

Methods: Six male dogs (23.3±1.5 kg) were each studied on two consecutive days. On both days, 40 mg unlabelled propranolol and 200 µCi of 3-H propranolol were simultaneously administered into the portal and femoral vein respectively via chronically implanted catheters. Arterial blood samples were taken 2, 4, 6, 8 and 10 min after propranolol administration and then at 15 min intervals for 4 hr. On the first day the study was performed after a single IV dose of thiopental (30 mg/kg). 24 hours later the study was repeated after spinal anesthesia had been established following a single IV dose of thiopental (30 mg/kg): lumbar puncture was performed with an 18 G epidural needle, and an epidural catheter was inserted into the subarachnoid space. Spinal anesthesia was established with 1.3 - 1.5 ml tetracaine (10 mg per 1 ml of 10% dextrose), and the extent of blockade was assessed by sensory and motor testing. Supplemental doses of tetracaine were given when evidence of block regression was noted. The mean total dose of tetracaine was 20.7±0.6 mg. When the sensory block was noted to extend from the mid-thoracic to the low sacral region, 3-H and unlabelled propranolol were administered as described above. Unlabelled propranolol concentrations were measured by HPLC and 3-H propranolol by liquid scintillation counting of the HPLC eluant corresponding to each propranolol peak. Portal clearance (Clp) and systemic clearance (Cls) were calculated as Dose/AUC where AUC is the area under the appropriate concentration-time curve. For a drug given intraportally and completely metabolized by the liver, portal clearance is numerically equal to intrinsic clearance (Clint), the intrinsic ability of the liver to metabolize drug, and is independent of liver blood flow. Volume of distribution (Vdß) was calculated as Cls/Kel where Kel is the elimination rate constant, and hepatic plasma flow (HPF) as Clp.Cls/Clp-Cls. The results were analyzed by Student's t-test for paired data or Wilcoxon sum rank test as appropriate and p<0.05 taken as the minimum level of significance. Approval of the Animal Care Committee was obtained.

Results: Mean plasma propranolol concentrations following intraportal and intravenous administration are shown in the Figure. There was no significant difference in the intrinsic clearance during spinal anesthesia compared to control (Table), indicating that spinal anesthesia had no effect on liver drug metabolism. Similarly, spinal anesthesia did not significantly effect either systemic clearance or hepatic plasma flow, although they were 22 and 27% lower respectively during the spinal anesthetic as compared to the control day (Table). Volume of distribution and elimination half-life were unchanged by spinal anesthesia (Table).

Discussion: This study has clearly shown that spinal anesthesia did not alter propranolol disposition. The intrinsic clearance of propranolol, which reflects the drug metabolizing capacity of hepatic enzymes, was unchanged by spinal anesthesia. This is in marked contrast to other anesthetic agents which profoundly inhibit drug metabolism. Over the four hour study period there was not an important fall in hepatic plasma flow, which combined with the unchanged drug metabolism resulted in no change in systemic clearance or elimination half-life. Thus, we conclude that spinal anesthesia has the least effect of all anesthetic agents on perioperative drug disposition.

FIGURE: MEAN PLASMA PROPRANOLOL CONCENTRATIONS

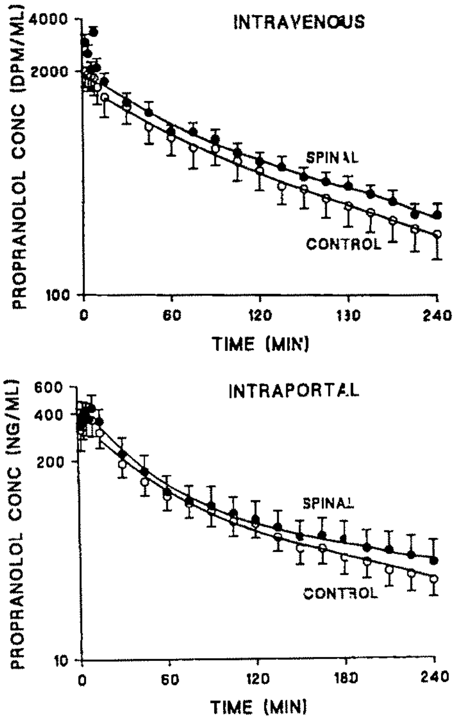

TABLE: EFFECT OF SPINAL ANESTHESIA ON PROPRANOLOL DISPOSITION (±SEM)

	Clint (1/min)	Cls (1/min)	T1/2B (1/min)	Vdß (1)	HPF (1/min)
CONTROL	2.01 ±0.75	0.9 ±0.23	104 ± 20	127 ± 27	2.4 ±0.6
SPINAL	1.9 ±0.7	0.7 ±0.12	112 ± 18	103 ± 14	1.75 ±0.4
SIGNIFICANCE	NS	NS	NS	NS	NS

Supported by Study Center Anesthesia Toxicology

Title A COMPARISON OF THREE METHODS TO REDUCE NAUSEA AND VOMITING AFTER ALFENTANIL ANESTHESIA IN OUTPATIENTS

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Introduction: Outpatient gynecologic procedures are often associated with a high incidence of postoperative nausea and vomiting (1,2). Droperidol and metoclopramide both alone and in combination, have been recommended to reduce these problems (1,3,4). Alfentanil, a short acting narcotic, often used for these procedures has been indicted as a cause of the nausea and vomiting. The purpose of this study was to compare three methods of pretreatment for reduction of nausea and vomiting after alfentanil anesthesia in outpatients undergoing laparoscopic procedures.

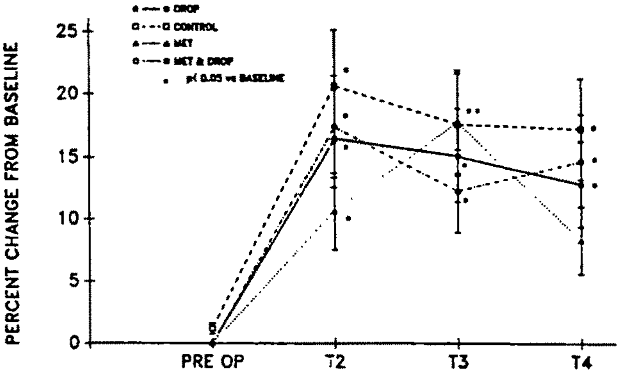
Methods: 44 ASA Class I-II female patients scheduled for laparoscopic procedures gave their informed consent to participate in this IRB approved study. The patients were randomly assigned to four groups: Group 1 --saline(S) as a control; Group 2 --droperidol(D) 15 µg/kg; Group 3 -- metoclopramide(M) 150 µg/kg, and Group 4--both droperidol and metoclopramide(D/M) in the above doses. All medications and glycopyrrolate 0.2 mg were given intravenously 15-30 minutes prior to the induction of general anesthesia. A standardized anesthetic technique consisted of vecuronium 0.01 mg/kg intravenously 2 mins prior to induction. Preoxygenation by mask was begun with thisdefasciculation. Alfentanil 20 µg/kg was given over 90 seconds. Induction was completed with thiopental 3-5 mg/kg and succinylcholine 1.5 mg/kg was given to facilitate endotracheal intubation. Anesthesia was maintained with 60-70% N_2O in 40-30% O_2 and alfentanil 7 µg/kg with or without thiopental 0.3-1 mg/kg in response to changes in vital signs or patient movement. Muscle relaxation was accomplished with vecuronium 0.05-0.1 mg/kg. Each patient's stomach was suctioned intermittantly during the operation. Neuromuscular blockade was reversed at the completion of surgery with 2.5 mg neostigmine and 0.5 mg glycopyrrolate. During the preopeative evaluation a standardized questionnaire was used to elicit history of motion sickness, nausea with hunger or anxiety, hiatal hernia and chronic sinus problems. Patients were evaluated in the recovery lounge by an observer blinded to the treatment medication. A linear analog scale was used by the patients to rate their level of nausea. Incidences of vomiting and the time to discharge from the surgical center were also rated. All evaluations were recorded approximatly every ½ hour while the patient was in the recovery area. A follow-up call was made to determine problems at home as well as ability to tolerate fluids and solids. Data was analyzed with frequency analysis and Cochran-Mantel-Haenzsel Test and two way ANOVA.

Results: There was no significant difference in any of the groups' demographics including age, weight, height. Patients were NPO for at least 10 hours prior to surgery. The duration of surgery and dose of alfentanil administered also were not different between the groups. There was an overall incidence of vomiting of 49%. When the groups were compared to one another, pretreatment with any of the medications either alone or in combination did not change the incidence of nausea or vomiting (Fig. 1). None of the demographic factors (i.e. history of hiatal hernia, nausea with anxiety, sinusitis, motion sickness) correlated with vomiting. Only 5 of 44 patients complained of nausea and 1/44 vomited at home after discharge. All patients were able to at least take liquids on the day of surgery, and all were on a solid diet the day following surgery.

Discussion: The incidence of nausea and vomiting after gynecologic surgery has been reported as high as 68% (5). The incidence with narcotic anesthesia may be greater than when narcotics are not included in the regimen (6). Alfentanil, a short acting narcotic, provides rapid onset and rapid recovery so that it is recommended for use in outpatients having short or moderate length procedures. Nausea and vomiting occurred in 49% of our patients having a laparoscopy with this alfentanil regimen which is similar to other findings (5). Our data also demonstrates that low dose droperidol, metoclopramide or the combination is ineffective as an anti-emetic when administered preoperatively. This agrees with the findings of Cohen. Increasing the dose of droperidol might prolong recovery as has been demonstrated by previous studies. In conclusion, the preoprative administration of droperidol, metoclopramide or droperidol and metoclopramide is not effective in preventing or reducing nausea and vomiting in outpatients given alfentanil for laparoscopic procedures.

	S	M	D	M/D
Vomiting	7/11	5/11	5/11	5/11

Fig.1- % CHANGE FROM BASELINE OF LINEAR ANALOGUE RATING OF NAUSEA



t_2=47 min, t_3=76 min, t_4=107 min after surgery

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TITLE : DO PULSE OXIMETERS WORK IN PATIENTS WITH ARRHYTHMIAS?

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INTRODUCTION: Arterial oxygen saturation estimated by cutaneous pulse oximetry (Sp02) has been compared with oxygen saturation by in vitro oximetry (%Hb02) (1). Non-normal sinus beats and rhythms may affect the accuracy of pulse oximetry because these beats may result in lower stroke volume, pulse volume and lower pulsatile signal strength. This study compared the agreement of Sp02 with %Hb02 in patients in normal sinus (NSR) with patients who were not in NSR. We also studied the effect of pulse deficit on Sp02 agreement with %Hb02.

METHODS: This study was approved by the institutional review board. Surgical Intensive Care Unit patients with pre-existing arterial catheters were eligible for study entry. Sp02 was measured with an Ohmeda 3700, software version M (Ohmeda, Boulder, CO). %Hb02 was measured with an IL 282 Co-oximeter (Instrumentation Labs, Lexington, MA). Non-normal sinus rhythm (non-NSR) was defined as an irregularly irregular rhythm (e.g. atrial fibrillation, multifocal atrial tachycardia) or frequent ectopy (more than 10 premature atrial contractions or premature ventricular contractions per minute). Five or less ectopic beats per minute were considered NSR.

Before Sp02 was recorded, a stable Sp02 for 1 minute with a signal strength greater than 5 pixels, and at least three consecutive pulsatile waveforms had to be present. Sp02 was recorded while a simultaneous radial artery blood sample was withdrawn which was immediately analyzed for %Hb02. Heart rate by EKG and pulse oximetry were also recorded. The pulse deficit (PD) was defined as the difference between the two. A one minute EKG rhythm strip recording during blood withdrawal was also made. The EKG rhythm and number of ectopic beats during this minute were determined by a physician who did not measure Sp02 or %Hb02. The mean difference between Sp02 and %Hb02 (bias) and the standard deviation of this difference (precision) were used to compare the NSR group with the non-NSR group. The (Sp02 - %Hb02) difference of patients with PD > 3 was similiarly compared. Unpaired Student's t-test was used to compare the NSR group with the non-NSR group. A p value less than 0.05 was considered statistically significant. Power analysis was used to minimize the possibility of falsely concluding that there was no difference between the two groups. (Type II error.)

RESULTS: One hundred and fifty-six consecutive patients with radial artery catheters were studied; 121 were NSR and 27 were non-NSR (more than 10 ectopic beats per minute [11] or irregularly irregular rhythms [16]). NSR Sp02 ranged from 80 to 99% (mean 93.8% ± 4.2) and NSR %Hb02 ranged from 82.8 to 97.3% (mean 93.7% ± 3.8). Non-NSR Sp02 ranged from 85 to 99% (mean 94.7% ± 3.4) and non-NSR %Hb02 ranged from 84.8 to 98.4% (mean 94.2% ± 3.1). NSR bias (Sp02 - %Hb02) was 0.4 ± 2.0. Non-NSR bias was 0.6 ± 2.0. There was no statistically significant difference between the NSR and non-NSR bias (Sp02 - %Hb02) (P > .5, power > .95; probability of type II error < .05). Adjusting for COHb did not alter the statistical significance.

There were 21 PD patients. There was no statistically significant difference in (Sp02 - %Hb02) between the PD patients and non-PD patients (p = .08).

DISCUSSION: Our results for both NSR and non-NSR groups are similiar to the mean difference in Sp02 and %Hb02 previously reported (2.7 ± 5.8%) (1). Sp02 agrees with %Hb02 as well in non-NSR as in NSR patients when Sp02 is stable, the signal strength is greater than 5 pixels, and at least three consecutive pulsatile plethysmograms are noted; Sp02 may not be necessarily reliable if these conditions do not exist.

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Title: EFFECTS OF ENFLURANE (E) ON HEPATIC BLOOD FLOW IN CHRONICALLY INSTRUMENTED DOGS

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Introduction. The effects of isoflurane (I) and halothane (H) on liver blood flow differ in chronically instrumented dogs.[1] With E, studies have only been performed in laparotomized animals basally anesthetized with barbiturates.[2,3] Surgery and barbiturates have been demonstrated to interfere with the regulation of hepatic blood flow.[1] We studied hepatic blood flow in awake and E-anesthetized (E 2.5% end-tidal) dogs by using chronically implanted pulsed Doppler flow probes.

Methods. In this study (protocol approved by the Baylor College of Medicine Animal Program) five healthy mongrel dogs were chronically instrumented as follows: a Tygon catheter in the abdominal aorta, an electromagnetic flow probe around the pulmonary artery, pulsed Doppler flow probes around the portal vein and hepatic artery. The use of a Doppler flow probe for measurement of hepatic and portal blood flows has been previously validated.[4] At least 10 days after surgery the animals were studied. After awake hemodynamic measurements, anesthesia was induced by mask. Animals were intubated and ventilated with a mixture of $E/N_2/O_2$ to maintain PaO_2 and $PaCO_2$ at awake levels. E was maintained at 2.5% end-tidal (infrared absorption technique) for at least 45 min before hemodynamic measurements were started. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), hepatic artery blood flow (HABF), and portal venous blood flow (PBF) were continuously recorded. Data were analyzed using Student's t test and are presented as mean ± SEM. Alpha was set at a level of 0.05.

Results. E in a concentration of 2.5 % end-tidal decreased MAP, CO, PBF and THBF. HABF remained essentially unchanged.

Discussion. E has been reported to decrease HABF in dogs.[2,3] In contrast, at similar concentrations of E our study showed no significant effect on HABF when compared to the awake state in chronically instrumented dogs. Consequently, we suggest that the decrease in HABF, as shown in the previous studies, is the result of the combined effects of barbiturates, E, and the presence of surgery. We conclude that despite a significant reduction in CO and MAP, HABF is maintained in the presence of 2.5% E.

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Table 1. Hemodynamics and Hepatic Blood Flow in Awake and Enflurane-anesthetized Dogs

	Awake	Enflurane 2.5%
HR (bpm)	80±2	95±8
MAP (mmHg)	107±5	70±2*
CO (L/min)	2.0±0.3	1.6±0.2*
HABF (ml/min)	110±25	105±31
PBF (ml/min)	456±89	323±72*
THBF (ml/min)	592±96	444±89*

MAP = mean arterial pressure; CO = cardiac output; HABF, PBF, and THBF = hepatic artery, portal, and total hepatic blood flow.
* P < 0.05 vs. awake

Title: PHARMACOKINETICS OF I-653, SEVOFLURANE, ISOFLURANE, AND HALOTHANE IN SWINE

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Introduction. I-653 is a new inhaled anesthetic with a blood/gas partition coefficient (0.42) smaller than that of all presently used volatile anesthetics, including the experimental anesthetic, sevoflurane (1,2). Consistent with this low solubility, recovery from anesthesia with I-653 is more rapid than with other volatile agents (3). I-653 also is more resistant to biodegradation than such agents (4). Thus I-653 should washin and washout more rapidly than other agents, and the amount of I-653 taken up during anesthesia should be recoverable during washout. To confirm these predictions, we undertook the following studies in swine.

Methods. With approval from our Committee on Animal Research, we administered I-653, sevoflurane, isoflurane, and halothane concomitantly for 30 min (at 0.15-0.5 MAC constant inspired concentration for each anesthetic) to five normocapnic (ventilation controlled) female swine [20±2 Kg (mean±SD); 3-4 months of age] who also received a basal anesthetic with pentobarbital. Using gas chromatography, we measured inspired (FI), end-tidal (FA), and mixed-expired (FM) anesthetic concentrations. Ventilation (VE) was measured with a spirometer. These measurements permitted calculation of washin (FA/FI) and uptake [(FI-FM)VE]. Washout of anesthetics was accomplished over approximately 3000 min using a non-rebreathing system which delivered oxygen-enriched air. We measured FA, FM, and VE, and calculated washout (FA/FAO, where FAO is the last end-tidal concentration obtained during washin) and elimination (FM•VE). We obtained an estimate of time constatnts by fitting a 5-compartment exponential equation to the washout data. Using mass balance, we calculated the recovery of anesthetics. Assuming that the unrecovered anesthetic was metabolized, these data gave a value for metabolism as a fraction of the volume of the individual anesthetic taken up. Metabolism of all agents was normalized to that of isoflurane (we assumed that metabolism of isoflurane was minimal). We used paired t-tests with Bonferroni corrections, analysis of variance with repeated measures, and Newman-Keuls test for multiple comparisons to determine whether differences existed among anesthetics.

Results. Washin was most rapid with I-653, followed by sevoflurane, isoflurane, and halothane ($p<0.008$)(Table 1). Washout was most rapid with I-653 and sevoflurane, followed by isoflurane and halothane ($p<0.03$). Except for the first compartment, the time constants for I-653 tended to be shorter than the time constants for the other agents (all of which had similar time constants for a given compartment except sevoflurane which differed from isoflurane for the second and third compartments) ($p<0.05$)(Table 2). No difference in normalized recovery was found for isoflurane versus sevoflurane (104±13%). I-653 tended to have a lower recovery (84±19%), but not significantly different from isoflurane as did halothane (75±12%)($p<0.05$).

Discussion. As predicted from relative blood solubility, the rates of washin and washout are most rapid with I-653. The shorter time constants of I-653 also indicate that I-653 also may have lower tissue/blood partition coefficients, a factor that would further explain the more rapid washin and washout. The shorter time constants and lower tissue/blood partition coefficients also are consistent with the more rapid recovery observed in rats (3).

The failure to recover proportionately as much I-653 as isoflurane was unexpected and may be a consequence of either an unsuspected metabolism of I-653 (that is not revealed by the formation of inorganic fluoride) or greater losses via skin and mucous membranes. In addition, the proportional recovery of halothane was greater than that seen in similar studies in humans (5). This relatively diminished metabolism of halothane may be the result of the basal level of pentobarbital anesthesia that was continued throughout the washout period.

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Table 1. F_A/F_I and F_A/F_{Ao} Values (Mean±SD; N = 5)

	1 min	5 min	10 min	30 min
Washin				
I-653	0.66±0.02	0.83±0.02	0.89±0.01	0.93±0.01
Sevo	0.63±0.05	0.79±0.03	0.85±0.02	0.90±0.02
Isof	0.49±0.05	0.67±0.03	0.75±0.03	0.82±0.01
Halo	0.31±0.05	0.44±0.04	0.52±0.04	0.62±0.05
Washout				
I-653	0.169±0.032	0.078±0.012	0.046±0.011	0.020±0.003
Sevo	0.191±0.034	0.093±0.009	0.058±0.008	0.028±0.007
Isof	0.254±0.038	0.146±0.016	0.097±0.013	0.043±0.002
Halo	0.334±0.056	0.226±0.034	0.159±0.021	0.076±0.009

Table 2. Time Constants (min) for 5 Compartments

Comp.	I-653	Sevo	Isof	Halo
1st	0.29±0.04	0.33±0.05	0.32±0.05	0.28±0.06
2nd	4.8±1.3	5.1±1.2	6.9±1.6	7.5±1.9
3rd	34±6	35±9	41±7	40±5
4th	177±33	209±42	223±45	227±46
5th	830±130	1320±330	1360±320	1520±480

Title: RECOVERY FOLLOWING PROPOFOL VS ISOFLURANE ANESTHESIA IN PROCEDURES LONGER THAN NINETY MINUTES

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Introduction. Propofol, diisopropyl phenol, is a new intravenous agent currently undergoing clinical trials in the United States. Several investigators have reported a significantly faster recovery rate following a propofol-based anesthesia for short surgical procedures (< 1 1/2 hours) when compared to either a barbiturate or isoflurane-based anesthetic (1-3). This study was designed to compare the recovery parameters between propofol and isoflurane based anesthetics in procedures lasting longer than 90 minutes.

Methods. This study was approved by the Committee for Human Investigation; written informed consent was obtained. ASA I-II patients, 18-70 years of age, were divided by random assignment into two groups of twenty each (n=40). All patients were premedicated with atropine 0.4mg IM. At three minutes prior to induction patients received 0.04mg/kg of atracurium and at one minute prior to induction 1mcg/kg of fentanyl IV. Anesthesia was induced with propofol 2.5mg/kg (Group I) or thiopental 5mg/kg (Group II). Tracheal intubation was facilitated with succinylcholine 1.5mg/kg. In Group I anesthesia was maintained with a propofol infusion at a rate of 0.2mg/kg/min for fifteen minutes, decreasing to a rate of 0.15mg/kg/min for an additional fifteen minutes, and then decreasing to a rate of 0.1mg/kg/min for the remainder of the procedure. In Group II, anesthesia was maintained with 0.2-2% end-tidal isoflurane. Nitrous oxide 60-70% was employed in both groups; atracuruim was used to provide muscle relaxation when indicated. Prior to premedication baseline psychomotor performances were obtained using the Track Tracer and the Trieger Dot Test. The patient was also shown and asked to identify six pictures presented on cards. At the end of anesthesia (EOA), time from EOA to response to verbal commands and time to orientation to time, place, and person were recorded. Recovery was assessed with the use of the Aldrete Score, administration of the Track Tracer, Trieger Test, and Picture Card Memory tests once the patient was oriented. Recovery from anesthesia was assessed by observers unaware of the anesthetic given. These observers were also asked to make a determination of the anesthetic employed (n=30). Statistical analyses included descriptive methods, student's t-test, frequency and Chi Square, and Repeated Measures Analysis of Variance. Significance was accepted when $p < 0.05$. Results are presented as the mean ± SEM.

Results. There were no significant differences between the groups with respect to age, weight, sex, race, ASA classification, smoking history or type of surgical procedure. Duration of anesthesia was 140.1 ± 11.4 minutes and 119.8 ± 11.9 minutes in Groups I and II respectively ($p > 0.05$). There were no significant differences between groups with respect to baseline performance on the Track Tracer, Trieger or Picture Card Memory tests. Times from end of anesthesia to response to verbal commands and to orientation in Group I were 6.7 ± 0.7 minutes and 26.3 ± 4.0 minutes respectively, compared to times of 9.8 ± 2.5 minutes and 37.1 ± 5.4 minutes respectively in Group II. Those differences were not statistically significant. The level of consciousness portion of the Aldrete Score was significantly higher in Group I on admission to the Recovery Room and at 30 minutes ($p = 0.009$ and $p = 0.01$). There were no significant difference in any other Aldrete Score parameters. There were no significant difference between the groups in performance with the Track Tracer or Picture Card Memory Tests during the study period. Trieger Test scores were significantly better in Group I at time of orientation and when repeated thirty minutes later ($p \leq 0.02$ at both times). This difference was not evident 60 minutes after orientation. Recovery observers were able to properly discern Group I patients in 12 of 15 cases and Group II patients in 11 of 15 cases. Five of 20 patients in Group I complained of nausea in the recovery room compared to 7 of 20 in Group II - not a significant difference.

Discussion. This study demonstrated that the use of a propofol-based anesthetic technique is associated a superior Aldrete consciousness score upon admission to the recovery room and at 30 minutes and is also associated with a superior performance with the Trieger Dot Test when compared to an isoflurane-based anesthetic in procedures lasting longer than ninety minutes. These results do not support previous recent reports in the literature (4,5). Based on patient appearance and how the patients performed the tests (not their scores) blinded observers were able to predict propofol and isoflurane anesthetized patients with an accuracy of 80% and 73.4% respectively ($p=0.01$). As assessed by parameters used in this study the data suggests that recovery from a propofol-based anesthetic is more rapid than that following an isoflurane-based anesthetic for procedures greater than 90 minutes in duration and that this objectively measured difference is also subjectively apparent to the blinded observer.

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Title: ALKALINIZATION OF BUPIVICAINE FOR PERIBULBAR BLOCK

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Introduction. Alkalinization of a mixture of lidocaine and bupivicaine (B) has been shown to improve onset time and spread of peribulbar anesthesia(1). A 0.75% solution of B can be used for ophthalmic anesthesia(2). We undertook a double-blinded, prospective randomized study to see if ph-adjusted B mixtures had a faster onset time and better spread when used for peribulbar anesthesia.

Methods. After IRB approval 35 patients gave written informed consent. All patients were scheduled for elective intraocular surgery with regional anesthesia and MAC. The only exclusion criteria was prior vitreo-retinal surgery. Patients were randomly divided into two groups to receive an injection from one of two solutions: B-Pl=10 ml of 0.75% (plain) Bupivicaine (Astra, Westborough MA) or B-pH=10 ml of 0.75% drawn from a 30 ml vial to which 0.15 meq of bicarbonate was added. To each group 150 u of hyaluronidase were added.

Patients were premedicated with 50-100 mcg of fentanyl and 0.5mg of droper idol IV. All blocks were done by one of the investigators (KZ), who was unaware of the mixture, with 8 to 9ml of anesthetic. One injection was at the inferior orbital rim and the second at the supratrochlear notch with a 25 ga needle inserted past the equator of the globe. Each patient had digital massage with gauze for 2 min. Extraocular muscle movement was evaluated in each quadrant at 1 min intervals for 20 min. The block was considered satisfactory when akinesia occurred (defined as movement of < 1mm). Supplemental blocks (with the same mixture) were done at 20 min in the case of residual movement. Adequate analgesia was determined by lack of response to incision of the conjuctiva. Adequacy of the lid block was assessed by the surgeon who was unaware of the anesthetic used.

During the course of the study vials representive of the lots of local used were selected. The pH of the resulting mixtures were measured by a Beckman model 4500 pH meter.

Differences between onset times of akinesia between groups were evaluated by a Students t-test. Need for supplemental injections was compared among groups by the Fisher exact test. A P of < 0.05 was used to reject the null hypothesis.

Results. 17 patients received B-Pl and 18 B-pH. Mean pH values (±SEM) and numbers of patients needing supplemental blocks at 20 min are presented in Table 1.

TABLE 1

	B-Pl	B-pH
pH	5.45±.12	6.82±.09
sup. block	5/17	1/18

Plain B had a higher need for supplementation which was statistically significant.

Mean time to akinesia in all quadrants (±SEM) is presented in Figure 1.

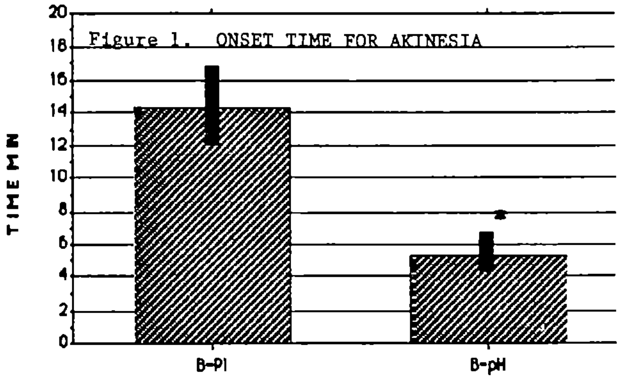
Figure 1. ONSET TIME FOR AKINESIA

Statistical analysis reveals that the B-pH group has faster onset than the B-Pl group (5.3±1.2 vs. 14.3±2.3 min - $p< 0.001$). All patients had adequate analgesia and lid akinesia for surgery.

Discussion. Alkalinization of local anesthetic solutions increases the amount of drug available in the non-cation form and presumably this increases nerve penetrance to decrease onset time. The results of our study show that alkalinization of 0.75% bupivicaine results in a more rapid onset and better quality block when this drug is used for peribulbar anesthesia.

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Title: FRESHLY ADDED EPINEPHRINE DOES NOT AFFECT THE ONSET TIME OF PH-ADJUSTED LIDOCAINE/BUPIVICAINE FOR PERIBULBAR ANESTHESIA

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Introduction. Alkalinization of local anesthetics has been shown to improve onset time and spread of anesthesia(1). In a previous study we demonstrated that alkalinized mixtures of lidocaine (L) and bupivicaine (B), or stock lidocaine with epinephrine (LE)/bupivicaine, improved the onset and quality of peribulbar anesthesia(2). However, the pH-adjusted LE/B mixture had a slower onset time than did the pH-adjusted L/B solution. We undertook a prospective, double-blinded, randomized study to see if freshly added E affected the onset time and quality of pH-adjusted L/B mixtures when used for peribulbar anesthesia.

Methods. After IRB approval of the Long Island College Hospital, 40 patients gave written informed consent. All patients were scheduled for elective intraocular surgery with regional anesthesia and MAC. The only exclusion criteria was prior vitreoretinal surgery. Patients were randomly divided into 2 equal groups of 20 to receive one of two possible L/B mixtures: LB= 5 ml of 2% L (Abbott labs) with 0.04 meq/ml sodium bicarbonate plus 5 ml of 0.75 % B (Astra, Westborough MA); or LBE= 5 ml of 2% L (with 0.04 meq/ml sodium bicarbonate) to which 10 mcg/ml of E was added plus 5 ml of 0.75% B. To 10 ml of each of the preceeding 150 units of hyaluronidase were added. Patients were premedicated with 50-100 mcg of fentanyl and 0.5 mg of droperidol IV. All blocks were done by one of the investigators (KZ), who was unaware of the mixture, with 8 to 9 ml of anesthetic. One injection was at the inferior orbital rim and the second at the supratrochlear notch with a 25 ga needle inserted past the equator of the globe. Each patient had digital massage with gauze for 2 min. Extraocular muscle movement was evaluated in each quadrant at 1 min intervals for 20 min. All blocks were done ½ to 3 hrs prior to surgery. The block was considered satisfactory when akinesia of the extraocular muscles occurred (defined as movement of <1mm). Supplemental blocks (with the same mixture) were done at 20 min in the case of residual movement. Adequate analgesia was determined by lack of response to incision of the conjuctiva. Adequacy of the lid block was assessed at the time of surgery by the surgeon who were unaware of the local anesthetic mixture used.

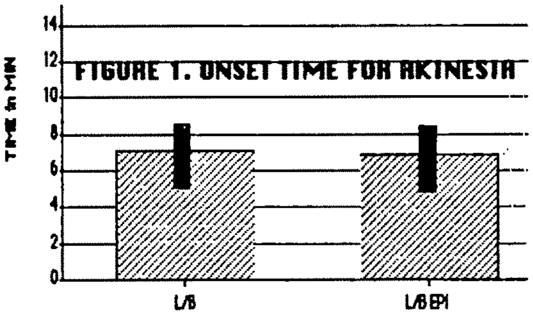
During the course of the study vials representative of the lots of local used were selected. The pH of the resulting mixtures were measured by a Beckman model 4500 pH meter. Differences between onset times of akinesia between groups were evaluated by the ANOVA. Need for supplemental injections was compared among groups by the Fisher exact test. A P of <0.05 was used to reject the null hypothesis.

RESULTS. Mean pH values (±SEM) and numbers of patients needing supplemental blocks at 20 min are presented in Table 1.

TABLE 1

	LB	LBE
pH	6.85±0.12	6.91±0.08
sup.block	3/20	2/20

There was no statistical difference in either solution in terms of pH or need for supplemental injections. Mean onset times (±SEM) for akinesia were similar for LB 7.1±1.6 vs. LBE 6.9±1.5 min (see Fig. 1).



All patients had adequate anesthesia and akinesia of the extraocular muscles and eyelids, and required no further injections for surgery.

Discussion. Many ophthalmologists prefer to use epinephrine containing local anesthetics for retrobulbar anesthesia. The addition of fresh epinephrine to the alkalinized mxture of lidocaine and bupivicaine had no effect on the resulting pH of the solutions. It is thought that E prevents vasodilatation and increased intraocular pressure that may occur with the local anesthetic. The onset time and quality of extraocular muscle blockade was equivalent in both groups. This study demonstrates that freshly added epinephrine does not adversely affect the onset time or quality of alkalinized Lidocaine/Bupivicaine mixtures when used for peribulbar block.

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Title:
LIDOCAINE IMPROVES INTUBATING CONDITIONS WITH VECURONIUM: A NEUROMUSCULAR AND HEMODYNAMIC STUDY

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Introduction. A common clinical problem in substituting a non-depolarizing muscle relaxant for succinylcholine in short ambulatory procedures is that published intubating doses often have a duration of action which may outlast the surgical procedure. Good to excellent intubating conditions have been reported with 72 μg/kg of vecuronium **(V)** (1). While others report that 100 μg/kg of **V** is needed to provide excellent intubating conditions at 3.5 min, with an average duration of 25 min (2). It is known that IV lidocaine **(L)** is an useful adjunct for endotracheal intubation. In addition to attenuating the tachycardic and hypertensive responses to laryngoscopy, **L** may also have muscle relaxing properties (3,4). We undertook a prospective, randomized study to evaluate the effects of **L** 3 mg/kg IV on the time to intubation, intubating conditions and duration of action with 72 μg/kg of **V**.

Methods. This protocol was approved by the IRB of the Long Island College Hospital and written informed consent was obtained from each subject. 16 ASA I-II patients aged 22 - 44 years were studied. Patients were brought to the OR unpremedicated. Anesthesia was induced with thiopental 6 mg/kg IV given over 90 s with the patients breathing N_2O/O_2 (1:1 ratio). Force of thumb adduction was measured and continuously recorded in response to a single supramaximal stimulus delivered at a rate of 0.1 Hz from surface electrodes over the ulnar nerve. Ventilation was controlled to keep the $ETCO_2$ normal. All patients then received 72 μg/kg of **V** and either saline (Group **V**) or **L** 3.0 mg/kg (Group **V/L**). The intubating anesthetist was unaware of the group assignment. Intubation was performed at 90% twitch depression and the time and conditions were noted (1= excellent or ideal; 2=good, cords move, patient coughs but does not move; 3= fair, poor relaxation, patient moves limbs; 4= unsatisfactory, intubation impossible). Mean arterial blood pressure (MAP) and heart rate (HR) were determined at control; 1 and 2 min after thiopental/**V**; 1 and 2 min after intubation (INT +1 or +2). Anesthesia was maintained with N_2O/O_2 (70/30%) and an alfentanil infusion. Time to recovery of the twitch to 25 % of control was noted and additional **V** was given as indicated.

Times to 90 and 100% twitch suppression and recovery to 25 % were analyzed by a Student's t-test for paired data. MAP and HR were analyzed using an ANOVA. A p of < 0.05 was considered significant. Intubation scores were subjected to a Mann-Whitney-U test.

Results. The times in min to 90 and 100% twitch suppression and recovery to 25 % of control are listed in Table 1. Hemodynamic data (HR in beats/min; MAP in mm Hg) are presented below in Table 2. Both groups had similar intubation scores.

Discussion. Our results show that 3 mg/kg of **L** decreased the onset time without prolonging the duration of **V**, 72 μg/kg. After intubation, both groups developed hypertension and tachycardia which was more severe in those who did not receive **L**. The results of this study support the use of lidocaine as an adjunct to vecuronium for endotracheal intubation. This combination may be useful for outpatient anesthesia.

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TABLE 1

	V	**V/L**	**p-value**
90%	3.02 ± .09	2.15 ± .17	< 0.01 *
100%	3.4 ± .09	2.5 ± .18	< 0.01 *
25 % rec.	24.9 ± 1.4	24.2 ± 2.4	.22 NS

ALL DATA ARE IN MIN, MEAN ± SEM. P < 0.05 FOR SIGNIFICANCE.

TABLE 2

TIME	**V-HR**	**V/L-HR**	**V-MAP**	**V/L-MAP**
Control	82 ± 2	84 ± 3	82 ± 1.4	88 ± 2.0
1 min	87 ± 2	87 ± 3	77 ± 2.2	87 ± 3.6
2 min	87 ± 2	86 ± 3	79 ± 2.5	86 ± 4.0
INT + 1	108 ±3*S	95 ± 2*	113 ±2.5*S	106 ± 5.6*
INT + 2	106 ±2*S	95 ± 2*	116 ±1.4*S	104 ± 5.1*

KEY: SEE METHODS. * DENOTES A VALUE THAT IS SIGNIFICANTLY DIFFERENT FROM CONTROL BY ANOVA (P <0.05). S DENOTES A MEAN THAT IS HIGHER THAN THE OTHER TREATMENT AT THE SAME TIME (P < 0.05).

Title:

MK-801, A GLUTAMATE ANTAGONIST, REDUCES ISOFLURANE MAC IN THE NEW ZEALAND WHITE RABBIT

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__Introduction__: Recently, there has been an increased interest in the ability of MK-801 to reduce ischemic neuronal injury.[1] MK-801 is a non-competitive antagonist of glutamate at central nervous system N-methyl-D-aspartate (NMDA) receptors. When administered to awake rabbits, MK-801 causes marked sedation. This suggests that MK-801 may also possess anesthetic properties. To investigate this possibility, we determined the effects of 0.1, 0.5, and 2.5 mg/kg of MK-801 on isoflurane (ISO) MAC, the electroencephalogram (EEG), mean arterial pressure (MAP) and heart rate (HR) in New Zealand white rabbits.

__Methods__: Following approval by the institutional animal care committee, 18 rabbits weighing approx. 3.2 kg were anesthetized with 4% ISO in oxygen in a plexiglass box. Tracheal intubation was accomplished without the use of muscle relaxants and the lungs were mechanically ventilated with 1.4% ISO to acheive an end-tidal CO_2 of 35-40 mmHg. A catheter was placed in a marginal ear vein for the administration of 0.9% saline (4 ml/kg/hr). A femoral artery was cannulated for continuous monitoring of MAP and intermittent sampling of arterial blood. Needle electrodes were placed in the scalp for the monitoring of the EEG. Esophageal termperature was servo-controlled to 37° C. Monitored variables included MAP, HR, end-tidal CO_2 and ISO concentrations, temperature, and the EEG. Following an equilibration period, all variables were recorded (t=0) and MK-801 (0.1, 0.5, or 2.5 mg/kg) was infused IV over a 5 minute period. All variables were again recorded upon completion of the infusion (t=5) and at 5 minute intervals for 15 minutes (t=10, 15, and 20). MAC was then determined using the tail clamp method of Eger et al.[2] Blood samples were obtained at the time of final tail clamping for determination of MK-801 levels. Although ISO MAC in New Zealand white rabbits has been previously reported to be 2.05 ± 0.19%, ISO MAC was determined in 3 additional animals which had not received MK-801 to verify these values. MAP and HR data following MK-801 administration were compared to pre-MK-801 values (t=0) with a repeated measures ANOVA followed by Dunnett's t tests. MAC values were examined using ANOVA followed by Scheffe's test for multiple comparisons. In all cases, p values < 0.05 were considered statistically significant.

__Results__: ISO MAC was 2.12 ± 0.19% (mean ± SD) in the three control animals that did not receive MK-801. ISO MAC was significantly decreased to 1.27 ± 0.32%, 1.10 ± 0.33%, and 0.70 ± 0.19% following the administration of 0.1, 0.5, and 2.5 mg/kg of MK-801 respectively (See fig. 1). Plasma levels of MK-801 ranged from 4.8 ± 1.2 µg/ml (0.1 mg/kg) to 106.0 ± 34.2 µg/ml (2.5 mg/kg) (See fig. 2). Examination of the EEG revealed the appearance of a burst-suppressed pattern following the administration of 0.5 and 2.5 mg/kg of MK-801. A high-frequency, low-amplitude activation pattern always accompanied tail clamping. At the 2.5 mg/kg dose, MAP fell significantly from control value although there was no significant change in HR.

__Discussion__: The glutamate antagonist MK-801 has been shown to decrease neuronal injury in an animal model of focal ischemia.[3] This study demonstrates that MK-801 also possesses significant anesthetic properties as evidenced by a dose-dependant reduction in ISO MAC associated with the appearance of a burst-suppressed EEG pattern. The decreases in MAP seen following the administration of MK-801 may be consistent with the production of a deeper plane of anesthesia or may reflect a direct hemodynamic effect of this drug.

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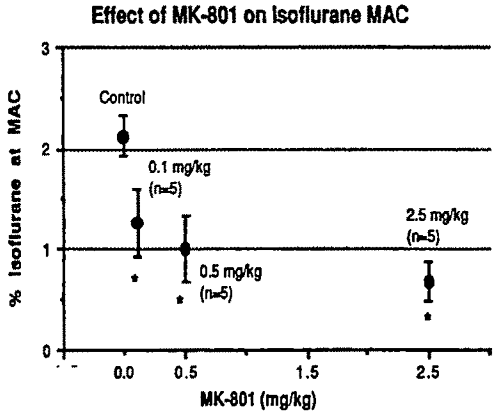

Figure 1. Effect of MK-801 (0.1, 0.5, and 2.5 mg/kg) on isoflurane MAC in New Zealand white rabbits (* = p < 0.05 vs. control).

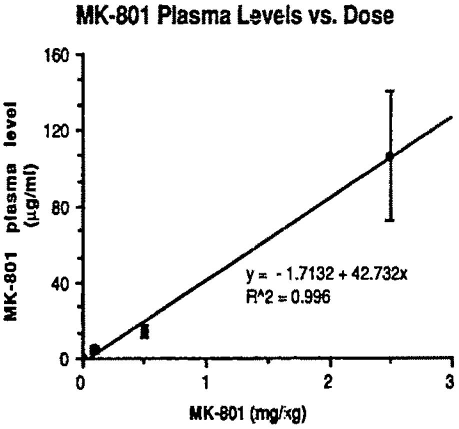

Figure 2. Plasma levels of MK-801 at MAC after 0.1, 0.5, and 2.5 mg/kg of MK-801.

Title: ANTAGONISM OF NEUROMUSCULAR BLOCK BY SEQUENTIAL VS. COMBINED USE OF GLYCOPYRROLATE AND PYRIDOSTIGMINE

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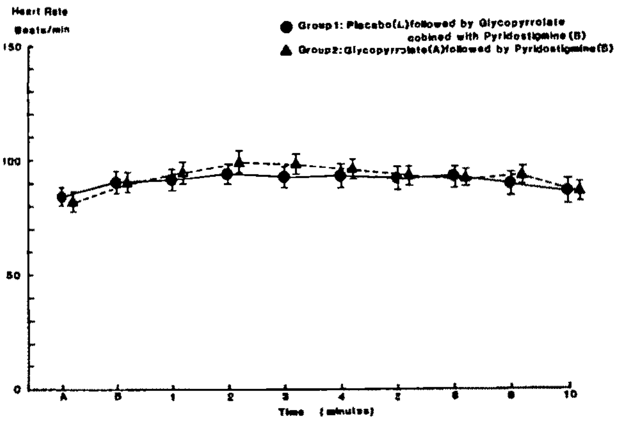
Introduction. The hemodynamic effects associated with the antagonism of neuromuscular block by either sequential or combined administration of glycopyrrolate and pyridostigmine have not been previously studied in a double-blind, randomized, parallel design. Therefore these investigations were undertaken.

Methods. 60 patients in ASA physical state I-II, who gave valid written consent and were scheduled to undergo upper abdominal surgery requiring profound muscle relaxation, e.g. cholecystectomy, were studied. Approval by the Institutional Review Board was obtained. According to a randomization schedule, 30 patients (Group I) (mean ± S.E.) age = 35.1 ± 2.3, mean ± S.E. weight = 71.2 ± 2.9 kg received the saline placebo, (Drug A) followed 4 min. later by 200.1 ± 1.4 μg/kg pyridostigmine and 8.1 ± 0.4 μg/kg glycopyrrolate (Drug B), if no greater than 10 beats increase in heart rate per min. occurred. In another 30 patients (Group II) (mean age = 38.7 ± 2.1 yrs.; mean weight = 70.9 ± 3.1 kg) glycopyrrolate, 8.0 ± 0.1 μg/kg (Drug A) was given first that usually increased heart rate more than 10 beats/min., when pyridostigmine, 199.0 ± 2.3 μg/kg (Drug B) was administered. The heart rate was continually monitored for 5 min. prior to the administration of Drug A and for at least 10 min. following the start of Drug B. The brachial arterial blood pressure was intermittently monitored by an oscillometric non-invasive, automated pressure monitor. The patients received only diazepam, 10 mg. p.o. and glycopyrrolate, 0.2 mg i.m. for preanesthetic medication. After thiopental induction, anesthesia was maintained by either enflurane (N = 35) or isoflurane (N = 25) in combination with N_2O-O_2. For muscle relaxation, either pancuronium (N = 40) or vecuronium (N = 20) was used in doses sufficient to provide 95% neuromuscular block. When all surgical stimuli ceased, the inhalation agent was eliminated and the hemodynamic parameters stabilized, the antagonism of the neuromuscular block was carried out. The times from completion of Drug B injection to the recovery of the first twitch of the train of four response to 95% and to 75% of T_1/T_4 were evaluated from the intermittently recorded train of four responses by a force-transducer at 5 sec. intervals. ECG abnormalities and excessive secretions and other side effects were also recorded.

Results. The mean ± S.E. heart rates were 84.4 ± 3.3/min. in Group I and 82.3 ± 3.0/min. in Group II. No significant difference in heart rate was observed between Group I and II at any time following Drug A and Drug B. The time intervals to 95% recovery of T_1 in T_1/T_4 were 4 min. 30 sec. ± 2.8 sec. and 5 min. 11 sec. ± 4.8 sec. in Groups I and II ($p < 0.01$). The time intervals to 75% recovery of T_1/T_4 were 5 min. 47 sec. ± 3.9 sec. and 6 min. 29 sec. ± 4.6 sec. for Groups I and II. These differences were not significant, although the T_1/T_4 ratio did not differ; these were 0.33 ± 0.04 and 0.30 ± 0.04 in Groups I and II. The systolic blood pressure increases were identical in Group I and II, 145.8 ± 4.1 mmHg and 142.7 ± 3.1 mmHg resp. The systolic blood pressure decreases were also identical in Groups I and II; 118.2 ± 2.8 mmHg and 119.7 ± 2.6 mmHg resp. (N.S.). No significant changes were observed in diastolic blood pressure in either group during antagonism of neuromuscular block. Junctional rhythm was observed in 3 patients in Group I. No other arrythmias, hypersecretion or bronchospasm was observed in any of the patients in either of the groups. The time to complete reversal of the neuromuscular blocks were identical; 9.6 ± 0.8 min. in Group I and 9.2 ± 0.8 min. in Group II (N.S.).

Discussion. Either sequential or combined administration of glycopyrrolate and pyridostigmine antagonized completely the neuromuscular block induced by either pancuronium or vecuronium in less than 10 min. The combination of glycopyrrolate with pyridostigmine resulted in more rapid recovery of T_1 to 95% than sequential administration. Although no changes in heart rate and blood pressure occurred in either group, 3 patients developed junctional rhythm with the mixture of glycopyrrolate and pyridostigmine used in Group I. No hypotension, bronchospasm and excessive secretions were observed in either group.

HEART RATE CHANGES DURING ANTAGONISM OF NEUROMUSCULAR BLOCK



Title: ARE CLINICIANS OR RESEARCHERS BETTER TEACHERS?

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Skilled communication, clinical expertise, knowledge of the literature, and competent role model are essential characteristics of an effective teacher. In many Departments of Anesthesiology, these roles in post-graduate residency education are met by two types of faculty: clinicians and researchers. Each brings his/her own strengths to bear upon the quality of resident training. Is it possible to discern which faculty group, researchers or clinicians, is perceived as superior educators by anesthesia trainees?

METHODS. Data was tabulated from the 3726 annual faculty evaluations by the anesthesiology residents for the years 1986-88. These objective evaluations required scoring (0-5 points) for each of seven factors:

1. Enjoyable to work with
2. Peri-operative teaching
3. Care for personal needs (e.g. breaks, reliefs, etc)
4. Back-up for complicated patients
5. Back-up on call
6. Didactic teaching
7. Overall contribution to the training program

The evaluations performed in January of each year, were coded as to resident and faculty member. Complete anonymity was maintained as to the identity of the resident evaluator. Faculty were defined as researcher or clinician on the following basis. A researcher is a physician faculty member who has: (1) independent funding for research greater than the proportional equivalent of one day's salary or (2) has had 2 research publications in peer reviewed journals during the study period or (3) principal investigator of 2 papers/year presented at national scientific meetings. A clinician is a physician who is primarily involved in the administration of clinical care and residency training. Data are presented as mean +/- SD. Group (unpaired) t tests were used for statistical analysis; $P < 0.001$ considered significant.

RESULTS. During the years 1986-1988, seventy-four (N = 74) residents submitted 3726 evaluations of 45 faculty members. On the basis of the definition,31 faculty were designated as clinicians (C) and 14 as researchers (R). In all three study years, the researchers were perceived as better teachers (Table). For example, factor 7 (overall contribution) was > 4.10 for researchers and < 4.00 for clinicians ($P < 0.001$). Analysis of the subset of faculty who were evaluated during the entire study period (all 3 years) shows similar results. In the subspecialties, (OB, Cardiac/Peds, the VA) researchers were perceived as better teachers. However, the General team is unique, in that clinicians were rated as better educators. As the residents progressed through the training program, they recorded a progressive number of factor differences between the two faculty groups (R > C): CA-1 = 0, CA-2=2 (Factors 4,6), CA-3 = 3 (Factors 2,5,6).

DISUCSSION. By use of a large data base of objective resident evaluations of faculty over a three year period (1986-88), it appears that researchers were perceived as better teachers than clinicians. However, even in this large sample, clinicians were found to make an important contribution to resident training. First, the General team anesthesiologists who were clinicians were rated extremely favorably. In addition it was not until the more advanced years of training,that residents reported any difference between researchers and clinicians. Other factors, not evaluated in the annual faculty review may also play a significant role in residency education. In summary, resident derived data suggests that physician researchers have an important role in post-graduate anesthesia education.

TABLE

Resident Evaluation of Faculty
(0-5 Scoring Scale)
Mean Values #

Factor		1986		1987		1988	
1	C	4.08	NS	4.11	NS	4.10	NS
	R	4.14		3.94		3.94	
2	C	3.82*		3.75*		3.86*	
	R	4.31		4.25		4.19	
3	C	3.92	NS	3.91	NS	3.83	NS
	R	4.05		3.87		3.89	
4	C	3.96*		3.98*		3.97*	
	R	4.44		4.37		4.32	
5	C	4.09*		4.01*		4.03	NS
	R	4.42		4.28		4.19	
6	C	3.77*		3.61*		3.81*	
	R	4.39		4.34		4.26	
7	C	3.88*		3.84*		3.95*	
	R	4.39		4.25		4.16	

Legend:
R = researcher
C = clinician
* = $P < 0.001$
NS = not significant
# = For clarity SD omitted

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TRACRIUM® INJECTION
(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:
Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

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[1] Miller R, Rupp S, Fisher D, et al: Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984;61:444–453.
[2] Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects.* Orlando, Grune & Stratton, 1984, p 98.
[3] Eagar B, Flynn P, Hughes R: Infusion of atracurium for long surgical procedures. *Br J Anaesth* 1984;56:447–452.

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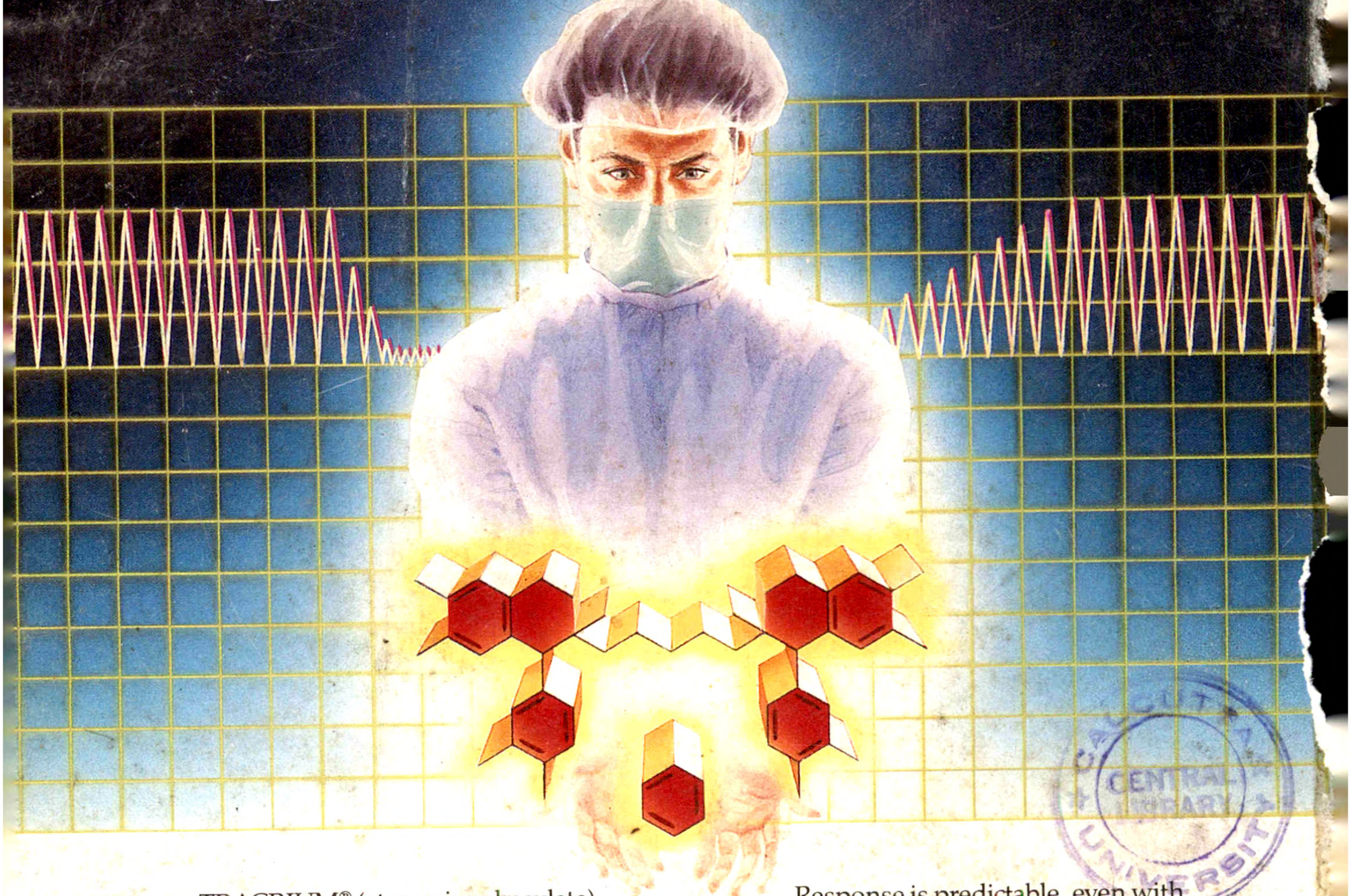

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9 JAN 1990

TRACRIUM® INJECTION

(atracurium besylate)

See brief summary of prescribing information on next page.

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